

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND
COUNTER DESIGNATIONS FOR BRUCE MCCARTHY, M.D.**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached deposition designations and counter-designations for the September 29, 2006 and March 16, 2007 depositions of Bruce McCarthy, M.D., former Medical Director and Head of the Analgesia Venture (ABT-594).

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: /s/ Eric J. Lorenzini
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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008.

/s/ Ozge Guzelsu

Bruce McCarthy Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce	6:5-11:18					
09/29/06	McCarthy, Bruce	13:1-14:12					
09/29/06	McCarthy, Bruce			14:13-14:17			
09/29/06	McCarthy, Bruce			14:21-15:2			
09/29/06	McCarthy, Bruce	15:3-16:16					
09/29/06	McCarthy, Bruce			16:17-16:21			
09/29/06	McCarthy, Bruce			16:25-17:6			
09/29/06	McCarthy, Bruce	17:7-18:8					
09/29/06	McCarthy, Bruce			18:13-18:24			
09/29/06	McCarthy, Bruce	18:25-19:7	19:9-19:11				
09/29/06	McCarthy, Bruce	19:12-20:15					
09/29/06	McCarthy, Bruce	21:17-24:2					
09/29/06	McCarthy, Bruce	24:22-25:22					
09/29/06	McCarthy, Bruce			26:12-26:13			
09/29/06	McCarthy, Bruce	29:25-32:14					
09/29/06	McCarthy, Bruce	33:8-35:5					

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce			35:14-35:21			
09/29/06	McCarthy, Bruce			39:5-39:7			
09/29/06	McCarthy, Bruce	40:20-41:7					
09/29/06	McCarthy, Bruce	42:2-45:6	45:7-45:10		3	BT	
09/29/06	McCarthy, Bruce	42:2-45:6	45:15-45:17				
09/29/06	McCarthy, Bruce	45:18-45:25					
09/29/06	McCarthy, Bruce	46:16-47:2					
09/29/06	McCarthy, Bruce	49:25-51:2	51:12-52:1				
09/29/06	McCarthy, Bruce	52:10-52:14					
09/29/06	McCarthy, Bruce	53:21-54:1			6	BV	
09/29/06	McCarthy, Bruce	54:17-55:19	55:20-56:18		6	BV	
09/29/06	McCarthy, Bruce	58:3-58:12			6	BV	
09/29/06	McCarthy, Bruce			60:2-60:10			
09/29/06	McCarthy, Bruce	65:16-66:13			10	CB	
09/29/06	McCarthy, Bruce			70:15-70:21			
09/29/06	McCarthy, Bruce			71:7-71:15			
09/29/06	McCarthy, Bruce			71:23-73:12			
09/29/06	McCarthy, Bruce	74:24-75:21					

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce			77:17-79:2			
09/29/06	McCarthy, Bruce	79:7-81:21			12	HN	
09/29/06	McCarthy, Bruce	85:25-88:5	88:6-88:17		14	CE	
09/29/06	McCarthy, Bruce	89:8-90:8			14	CE	
09/29/06	McCarthy, Bruce			90:9-90:23			
09/29/06	McCarthy, Bruce			97:9-97:21			
09/29/06	McCarthy, Bruce			97:22-99:13			
09/29/06	McCarthy, Bruce	100:21-104:18	104:20-104:24		18	CR	
09/29/06	McCarthy, Bruce	105:1-107:25			19	CV	
09/29/06	McCarthy, Bruce			109:16-110:17			
09/29/06	McCarthy, Bruce	113:3-113:11					
09/29/06	McCarthy, Bruce	117:7-119:6	119:22-119:25		21	DH	
09/29/06	McCarthy, Bruce	120:17-124:23			22	DL	
09/29/06	McCarthy, Bruce	128:23-131:3			25	DP	
09/29/06	McCarthy, Bruce	131:23-134:1			25	DP	
09/29/06	McCarthy, Bruce	135:5-137:4	137:6-137:11				
09/29/06	McCarthy, Bruce	139:21-139:25					
09/29/06	McCarthy, Bruce	142:10-142:22			27	DU	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce	144:1-144:6			27	DU	
09/29/06	McCarthy, Bruce	145:18-147:18	147:19-148:6				
09/29/06	McCarthy, Bruce			150:20-152:2			
09/29/06	McCarthy, Bruce			152:18-153:4			
09/29/06	McCarthy, Bruce			153:15-154:18			
09/29/06	McCarthy, Bruce	155:1-155:18	154:19-154:25				
09/29/06	McCarthy, Bruce	155:1-155:18	155:25-158:2				
09/29/06	McCarthy, Bruce			158:3-159:17	29		584
09/29/06	McCarthy, Bruce	160:2-160:22			30	ED	
09/29/06	McCarthy, Bruce			161:13-162:19			
09/29/06	McCarthy, Bruce			164:1-165:5			
09/29/06	McCarthy, Bruce			170:1-170:6			
09/29/06	McCarthy, Bruce			171:2-171:7			
09/29/06	McCarthy, Bruce			173:21-173:24			
09/29/06	McCarthy, Bruce	181:11-183:23	183:24-185:7		37	EL	
09/29/06	McCarthy, Bruce	185:9-188:8	188:9-189:4		37	EL	
09/29/06	McCarthy, Bruce			189:23-190:10			
09/29/06	McCarthy, Bruce			190:17-191:1			

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce			191:8-191:22	38		1112
09/29/06	McCarthy, Bruce			192:19-195:19			
09/29/06	McCarthy, Bruce			199:22-203:9			
09/29/06	McCarthy, Bruce	203:10-204:8	208:16-208:25		41	EW	
09/29/06	McCarthy, Bruce	211:18-217:25	218:1-218:1		42	EY	
09/29/06	McCarthy, Bruce	218:13-221:3	221:4-221:14		43	FF	
09/29/06	McCarthy, Bruce	218:13-221:3	222:14-224:14		43	FF	
09/29/06	McCarthy, Bruce	218:13-221:3	225:23-226:7				
09/29/06	McCarthy, Bruce			229:24-230:19			
09/29/06	McCarthy, Bruce			231:24-232:24			
09/29/06	McCarthy, Bruce	232:25-233:17			46	FK	
09/29/06	McCarthy, Bruce	234:3-234:15			46	FK	
09/29/06	McCarthy, Bruce			236:20-236:24			
09/29/06	McCarthy, Bruce	237:9-237:24	237:25-239:11		47	FN	
09/29/06	McCarthy, Bruce	241:23-243:21	243:22-244:2		47	FN	
09/29/06	McCarthy, Bruce	244:3-244:13			48	FZ	
09/29/06	McCarthy, Bruce	245:8-245:24			48	FZ	
09/29/06	McCarthy, Bruce	246:9-247:12	247:15-247:25		48	FZ	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
09/29/06	McCarthy, Bruce	248:20-248:22					
09/29/06	McCarthy, Bruce	248:20-248:22	249:6-249:9				
09/29/06	McCarthy, Bruce	248:20-248:22	249:22-250:12				
09/29/06	McCarthy, Bruce			256:5-256:17			
09/29/06	McCarthy, Bruce			257:8-257:16			
09/29/06	McCarthy, Bruce			258:9-258:17			
09/29/06	McCarthy, Bruce	259:2-260:4			52	FX	
09/29/06	McCarthy, Bruce			263:13-265:18	54		661
09/29/06	McCarthy, Bruce			266:2-266:16			
09/29/06	McCarthy, Bruce			270:2-271:21			
09/29/06	McCarthy, Bruce			272:5-272:18			
09/29/06	McCarthy, Bruce	274:6-277:13	277:15-278:9		59	HO	
09/29/06	McCarthy, Bruce	274:6-277:13	278:22-279:5				
09/29/06	McCarthy, Bruce	279:6-280:17			60	HM	
09/29/06	McCarthy, Bruce	279:6-280:17		280:18-281:12	61		1113
09/29/06	McCarthy, Bruce	283:9-284:12	284:13-284:24		63	HP	
09/29/06	McCarthy, Bruce	284:25-285:18			63	HP	
03/16/07	McCarthy, Bruce	4:1-4:10					

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
03/16/07	McCarthy, Bruce	14:25-15:14			66	BW	
03/16/07	McCarthy, Bruce	16:25-19:1	19:2-19:23		66	BW	
03/16/07	McCarthy, Bruce	22:10-22:24	23:3-23:6		66	BW	
03/16/07	McCarthy, Bruce	24:22-25:11	26:10-26:23		67	BZ	
03/16/07	McCarthy, Bruce	27:21-29:12			67	BZ	
03/16/07	McCarthy, Bruce			29:18-30:13			
03/16/07	McCarthy, Bruce			32:16-33:22			
03/16/07	McCarthy, Bruce	35:13-35:23			71	CH	
03/16/07	McCarthy, Bruce	37:6-42:13	42:14-43:10		71, 72	CH, CJ	
03/16/07	McCarthy, Bruce	43:11-43:17			72	CJ	
03/16/07	McCarthy, Bruce	52:4-54:10			75	DC	
03/16/07	McCarthy, Bruce	57:16-63:18			77	CN	
03/16/07	McCarthy, Bruce			67:2-67:25			
03/16/07	McCarthy, Bruce	72:23-74:4	74:15-75:19		82	DE	
03/16/07	McCarthy, Bruce	78:8-79:1			84	DM	
03/16/07	McCarthy, Bruce	79:21-82:15	79:18-79:20		84	DM	
03/16/07	McCarthy, Bruce			97:8-99:6			
03/16/07	McCarthy, Bruce	99:8-100:9	102:8-103:3		91	DZ	

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
03/16/07	McCarthy, Bruce	103:5-103:23	103:24-107:7		92	EA	
03/16/07	McCarthy, Bruce	103:5-103:23	107:24-108:5				
03/16/07	McCarthy, Bruce	103:5-103:23	108:17-108:24				
03/16/07	McCarthy, Bruce	103:5-103:23	109:22-110:3				
03/16/07	McCarthy, Bruce	110:7-111:20	111:21-112:7		93	EC	
03/16/07	McCarthy, Bruce			124:20-125:4			
03/16/07	McCarthy, Bruce			126:3-126:5			
03/16/07	McCarthy, Bruce			141:13-141:23			
03/16/07	McCarthy, Bruce	141:25-144:6	145:6-145:13		103	EP	
03/16/07	McCarthy, Bruce	150:22-152:13			107	21	
03/16/07	McCarthy, Bruce			156:3-156:10			
03/16/07	McCarthy, Bruce			158:3-158:13			
03/16/07	McCarthy, Bruce	160:19-163:13			113	FT	
03/16/07	McCarthy, Bruce			166:15-169:9			
03/16/07	McCarthy, Bruce	171:10-172:12			118	GO	
03/16/07	McCarthy, Bruce			172:13-172:19			
03/16/07	McCarthy, Bruce	174:7-175:20	175:21-175:24		119	GR	

Color Key to Deposition Designations

 Designation by Plaintiffs

 Counter Designation by Defendants

 Designation by Defendants

McCarthy, M.D., Bruce Gerald (Linked) 9/29/2006 9:00:00 AM

1 UNITED STATES DISTRICT COURT

2 FOR THE

3 DISTRICT OF MASSACHUSETTS

4

5 JOHN HANCOCK LIFE INSURANCE

6 COMPANY, JOHN HANCOCK VARIABLE

7 LIFE INSURANCE COMPANY, and

8 MANULIFE INSURANCE COMPANY

9 (f/k/a INVESTORS PARTNER

10 INSURANCE COMPANY),

11 Plaintiffs,

12 vs Civil Action No. 05-11150-DPW

13 ABBOTT LABORATORIES,

14 Defendant.

15 _____/

16

17

18 DEPONENT: BRUCE GERALD MCCARTHY, M.D.

19 DATE: Friday, September 29, 2006

20 TIME: 9:00 a.m.

21 LOCATION: 350 South Main Street, Suite 400

22 Ann Arbor, Michigan

23 REPORTER: Angela E. Broccardo, CSR 4679

24

25

McCarthy, M.D., Bruce Gerald (Linked) 9/29/2006 9:00:00 AM

1 APPEARANCES:

2

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8 Appearing on behalf of the Plaintiffs.

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16 Appearing on behalf of the Defendant.

17

18

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McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Ann Arbor, Michigan

2 Friday, September 29, 2006

3 9:00 a.m.

4 * * *

5 BRUCE GERALD MCCARTHY, M.D.,

6 having first been duly sworn, was examined and

7 testified as follows:

8 EXAMINATION

9 BY MR. DAVIS:

10 Q. Good morning.

11 A. Good morning.

12 Q. Dr. McCarthy, my name is Brian Davis. I'm an

13 attorney representing John Hancock in litigation

14 with Abbott Labs involving the research funding

15 agreement that the parties entered into back in

16 March of 2001.

17 I'm going to ask you a series of

18 questions here today. If at any point in time

19 you don't understand any of my questions, please

20 just say so, and I'll try to rephrase them and

21 make them clear. Do you understand that?

22 A. Yes.

23 Q. And if you respond to my questions, I'm going to

24 assume that you understood them. Is that fair?

25 A. Yes.

1 Q. And if at any point in time you need to take a
2 break, please let us know, we'll try to
3 accommodate you as quickly as possible. Do you
4 understand that?

5 A. Yes.

6 Q. The only other ground rules I'll lay is -- you
7 are doing fine so far. You have to verbalize
8 your responses, and please let me finish my
9 question before you begin to respond. It makes
10 for a much cleaner transcript.

11 Would you state your name, please, for
12 the record?

13 A. Bruce Gerald McCarthy.

14 Q. Where do you live?

15 A. Ann Arbor.

16 Q. Street address, please?

17 A. 1355 Burgundy Road.

18 Q. How long have you lived there?

19 A. Two years.

20 Q. Where are you employed?

21 A. Pfizer.

22 Q. The pharmaceutical company?

23 A. Yes.

24 Q. What do you do for Pfizer?

25 A. Neuroscience clinical development.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. How long have you worked for Pfizer?

2 A. Two years.

3 Q. Before you worked for Pfizer, where did you

4 work?

5 A. Abbott Labs.

6 Q. What is your business address currently? Where

7 is your office?

8 A. Can I look at my card?

9 Q. Sure. Go right ahead.

10 A. Eastern Point Road is the only street address,

11 Mail Stop 8260-2319, Groton, Connecticut, 06340.

12 Q. Briefly, I just want to discuss your educational

13 background.

14 A. Uh-huh.

15 Q. Where did you go to high school?

16 A. West Linn, Oregon.

17 Q. West Linn, Massachusetts?

18 A. Oregon.

19 Q. Oh, West Linn, Oregon. Where did you go to

20 college?

21 A. Stanford University.

22 Q. When did you graduate?

23 A. 1988.

24 Q. With what degree?

25 A. Bachelor's of science.

1 Q. Did you go on to school from there?

2 A. Yes.

3 Q. To where?

4 A. Johns Hopkins School of Medicine.

5 Q. Did you graduate?

6 A. Yes.

7 Q. What year?

8 A. 1993. Wait. Yes, that's right.

9 Q. With what degree?

10 A. Medical degree.

11 Q. Are you licensed to practice medicine?

12 A. Yes.

13 Q. In what states?

14 A. Illinois, with a license in California that's

15 on -- I don't know what you call it. I'm trying

16 to think of the terminology. It's on -- I'm

17 trying to think of the word -- inactive status.

18 Q. Do you have an area of specialty?

19 A. Neurology.

20 Q. When were you first licensed to practice

21 medicine?

22 A. 1993.

23 Q. Same year you graduated from Johns Hopkins?

24 A. Yes.

25 Q. Dr. McCarthy, would you give me a brief

- 1 description of your educational background since
- 2 you graduated from Johns Hopkins, please?
- 3 A. I did my --
- 4 Q. I'm sorry, I meant your employment background
- 5 since you graduated from Johns Hopkins?
- 6 A. I was employed by the University of California
- 7 San Francisco in a medical internship from 1993
- 8 to 1994, and by the University of California San
- 9 Francisco in a neurology residency from 1994 to
- 10 1997, and then hired by Abbott Labs.
- 11 Q. In 1997?
- 12 A. Uh-huh.
- 13 Q. Did you work for Abbott from 1997 to 2004?
- 14 A. That's correct, yes.
- 15 Q. What positions did you hold in Abbott, beginning
- 16 in 1997?
- 17 A. Associate medical director, medical director,
- 18 venture head.
- 19 Q. Any other positions?
- 20 A. The name for venture head changed to global
- 21 project head, but it was the same position.
- 22 Q. Were you a global project head when you left
- 23 Abbott in 2004?
- 24 A. Yes.
- 25 Q. Why did you leave Abbott?

1 A. For better opportunities to work on early stage
2 compounds. The early stage compounds in the
3 neuroscience portfolio had all been discontinued
4 for toxicology reasons at that time.

5 Q. You are saying in Abbott's portfolio?

6 A. Uh-huh.

7 Q. You have to say yes or no.

8 A. Yes.

9 Q. Thank you. You can also say maybe sometimes.

10 MR. PHILLIPS: You can answer whatever
11 way you wish or need to, but you have to answer
12 verbally.

13 BY MR. DAVIS:

14 Q. When you worked at Abbott, where physically did
15 you work?

16 A. Abbott Park, Illinois.

17 Q. For all of your positions that was true?

18 A. Yes.

19 Q. Did you prepare for your deposition here today?

20 A. Yes.

21 Q. How did you prepare?

22 A. With Greg Phillips yesterday.

23 Q. How long did you meet with Mr. Phillips for?

24 A. Approximately six hours.

25 Q. Did you speak with anyone at Abbott about your

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. I think we've got that in one of the boxes.

2 We'll get to that one.

3 Going back to positions at Abbott, what

4 were the duties and responsibilities that you

5 had when you were a medical director?

6 A. The design of clinical trials, the oversight of

7 clinical trials, and the report of results of

8 clinical trials, and the communication of those

9 clinical trials.

10 Q. Pretty much start to finish with respect to

11 overseeing -- helping to create and oversee and

12 implement clinical trials; is that fair?

13 A. Yes.

14 MR. PHILLIPS: May I ask a question of

15 clarification? You asked him about his duties

16 and responsibilities as a medical director.

17 Were you distinguishing between medical director

18 and associate medical director?

19 MR. DAVIS: Yes, I was.

20 MR. PHILLIPS: Did you understand that?

21 THE WITNESS: Yes.

22 MR. PHILLIPS: Fine.

23 BY MR. DAVIS:

24 Q. I'll go back and hit associate in a moment. Who

25 was your immediate superior while you were a

1 medical director at Abbott?

2 A. Chris Silber.

3 Q. Anyone else?

4 A. I don't remember.

5 Q. When you were medical director, were you working

6 in the analgesia venture?

7 A. I was working in the analgesia venture, yes.

8 Q. Was Mr. -- is it Dr. Silber?

9 A. Yes.

10 Q. Was Dr. Silber the head of the analgesia

11 venture?

12 A. Yes.

13 Q. Did you work in any other ventures as a medical

14 director?

15 A. Yes.

16 Q. What other ventures?

17 A. Psychopharmacology venture.

18 Q. Any others?

19 A. No.

20 Q. You had experience -- strike that.

21 While you were at Abbott, you had --

22 one of the compounds that you worked with was

23 ABT-594; is that correct?

24 A. Yes.

25 Q. Was that while you were a medical director in

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 the analgesia venture?

2 A. Yes.

3 Q. Going back for a moment to when you were an

4 associate medical director, how did your duties

5 vary from when you were a medical director?

6 A. They were the same.

7 Q. Same job, lower pay?

8 A. Yes.

9 Q. When you became a venture head, how did your

10 duties change?

11 A. I became responsible for the drug development

12 program in its entirety.

13 Q. When did you first become a medical director at

14 Abbott?

15 A. I don't remember.

16 Q. When did you first become a venture head?

17 A. I don't remember.

18 Q. Going back to 594 -- did you have any

19 responsibilities for ABT-594 while you were a

20 venture head?

21 A. Yes.

22 Q. Does that help you place in time when it was you

23 became a venture head?

24 A. No.

25 Q. What responsibilities did you have concerning --

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 when I refer to 594, you understand I'm

2 referring to ABT-594?

3 A. Yes.

4 Q. What responsibilities did you have for 594 while

5 you were a medical director?

6 A. The design of clinical trials, the oversight of

7 clinical trials, and the reporting of results

8 from the clinical trials.

9 Q. And while you were a venture head?

10 A. Same, and in addition oversight of the

11 nonclinical elements of the drug development

12 program.

13 Q. What are the nonclinical elements?

14 A. They include but aren't limited to formulation

15 and manufacturing, toxicology, regulatory and --

16 sorry, and regulatory elements.

17 Q. Did you have any responsibility for

18 out-licensing?

19 A. No.

20 Q. Did you have any involvement in out-licensing?

21 A. Yes.

22 Q. What involvement did you have in out-licensing

23 of 594, if any?

24 A. I don't remember.

25 Q. Did you have any involvement or responsibility

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 for 594 while you were an associate medical

2 director?

3 A. Yes.

4 Q. Who was your immediate superior when you were an

5 associate medical director?

6 A. Chris Silber.

7 Q. When is the first time that you can recall that

8 you had any responsibility for 594?

9 A. Within the first months of employment.

10 Q. Was that one of your first assignments at

11 Abbott?

12 A. Yes.

13 Q. What were you assigned to do at that time

14 concerning 594?

15 A. To support the design of future clinical trials

16 and to support the safety review of ongoing

17 clinical trials.

18 Q. 594 was a compound under development at that

19 point in time?

20 A. Yes.

21 Q. Had any clinical trials of 594 taken place

22 before you first became involved with that

23 compound?

24 A. I don't think so.

25 Q. Did you participate in phase I studies with

1 respect to 594?

2 A. Yes.

3 Q. Did you participate in any preclinical studies

4 regarding 594?

5 A. No.

6 Q. You also participated in some phase II studies

7 regarding 594?

8 A. Yes.

9 Q. In the phase I studies of 594, what role did you
10 play?

11 A. I remember safety oversight, but other than
12 that, I don't remember.

13 Q. Do you remember how many phase I trials and
14 studies of 594 you were involved with?

15 A. I can recall at least three.

16 Q. Can you identify them? Would you identify them,
17 please?

18 A. The first-in-man single-rising-dose study, the
19 multiple-rising-dose study, and a study to
20 evaluate tolerability with dose escalation with
21 either a soft elastic capsule or a hard gelatin
22 capsule.

23 Q. Those were all phase I studies; correct?

24 A. Yes.

25 Q. What is the difference between a phase I study

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 and a phase II study?

2 MR. PHILLIPS: Generally speaking?

3 MR. DAVIS: Generally speaking.

4 THE WITNESS: Generally speaking, phase

5 I studies are performed using healthy

6 volunteers, and phase II studies are performed

7 using patients with the disorder under study.

8 BY MR. DAVIS:

9 Q. And then you are familiar with phase III

10 studies?

11 A. Yes.

12 Q. What is your understanding of generally the

13 difference between phase II studies and phase

14 III studies?

15 A. Phase II studies are exploratory, and phase III

16 studies are confirmatory for safety and

17 efficacy.

18 Q. Have you received training in running clinical

19 trials?

20 A. Yes.

21 Q. Where did you receive your training?

22 A. At Abbott and at Pfizer.

23 Q. What training did you receive at Abbott? Let me

24 revise that. Did you receive any formal

25 training at Abbott? And by formal, I mean

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 classroom instruction, lectures, instruction --

2 receiving actual written instructional

3 materials, things of that nature.

4 A. I don't believe so.

5 Q. Is it fair to say you received on-the-job

6 training in running clinical trials at Abbott?

7 A. Yes.

8 Q. From who?

9 A. Chris Silber, David Morris, Marleen Verlinden,

10 John Leonard.

11 Q. Anyone else?

12 A. I don't remember.

13 Q. Who is John Leonard?

14 A. He was the vice president of development in the

15 pharmaceutical division of Abbott.

16 Q. Do you know Perry Nisen?

17 A. Yes.

18 Q. Who is Mr. Nisen?

19 A. When I knew him, he was the -- in the oncology

20 development group at Abbott.

21 Q. Was he a technical person? Was he an executive?

22 MR. PHILLIPS: Objection.

23 THE WITNESS: Yes.

24 BY MR. DAVIS:

25 Q. I'm sorry, I confused you. Do you know what

1 position he held?

2 A. I believe he was either venture head or -- I

3 can't remember the title.

4 Q. Was he a doctor?

5 A. I believe so.

6 Q. When is the last time you had any communication

7 with Perry Nisen?

8 A. Sometime before 19 -- sorry, sometime before

9 2004.

10 Q. Did he leave Abbott while you were still

11 employed at Abbott?

12 A. I don't remember.

13 Q. Do you know where he works today?

14 A. I believe he works for GlaxoSmithKline.

15 Q. Do you know where?

16 A. I believe in the Philadelphia area.

17 Q. Getting back to your involvement in 594, you

18 know that Abbott ran a phase IIb clinical study

19 for 594 targeted at neuropathic pain?

20 A. Yes.

21 Q. Diabetic neuropathic pain?

22 A. Yes.

23 Q. And did you play a role in that study?

24 A. Yes.

25 Q. What responsibilities did you have with respect

1 to that study?

2 A. Oversight of the design, the conduct and

3 interpretation and reporting of results.

4 Q. Now, that study was given a number by Abbott of

5 M99-114. Is that consistent with your

6 recollection?

7 A. Yes.

8 Q. If I refer to it as the 114 study, you know

9 which study I'm referring to?

10 A. Yes.

11 Q. After the 114 study was complete, Abbott decided

12 to cease the development of 594; is that right?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: Yes.

15 BY MR. DAVIS:

16 Q. You recall that there was a time when you were

17 notified that Abbott would not be further

18 developing 594? Is that consistent with your

19 recollection?

20 A. Yes.

21 Q. Approximately when was that?

22 A. Fourth quarter of 2001.

23 Q. Were you told at that point in time why it was

24 that Abbott had decided not to continue

25 developing 594?

1 A. Yes.

2 Q. First, who told you?

3 A. I don't remember.

4 Q. What were you told?

5 A. I don't remember specifics, but in general

6 terms, that the risk/benefit was not adequate to

7 further pursue development of the drug.

8 Q. To your knowledge, did the tolerability of 594

9 as demonstrated in clinical trials play any role

10 in Abbott's decision to terminate the

11 development of 594?

12 A. Yes.

13 Q. How so?

14 A. The benefit of the drug at doses -- the benefit

15 of the drug at doses did not outweigh the

16 liabilities from tolerability issues.

17 Q. And what did you understand to be the

18 liabilities with respect to tolerability?

19 A. Rates of -- or nausea and vomiting and

20 dizziness.

21 Q. Is another word for vomiting emesis?

22 A. Yes.

23 Q. In the course of developing or working on 594,

24 did you occasionally hear or make reference to

25 the emesis liability associated with that

1 compound?

2 A. Yes.

3 (Marked for identification

4 Deposition Exhibit No. 1.)

5 BY MR. DAVIS:

6 Q. Dr. McCarthy, I'm going to show you what has

7 been marked as Exhibit 1 at your deposition and

8 ask you to look at it for a moment and tell me

9 first, sir, if you think you've ever seen this

10 document before.

11 MR. PHILLIPS: You are not asking

12 him -- or are you asking him if he's seen the

13 particular copy with the handwriting on it?

14 MR. DAVIS: Any version of this

15 document, as best you recall.

16 THE WITNESS: Yes.

17 BY MR. DAVIS:

18 Q. What is this Exhibit 1?

19 A. It appears to be a framework for a decision

20 analysis for ABT-594 and backups and another

21 pharmacology, adenosine kinase inhibitor.

22 Q. First we'll do some terms here, if we may. 594,

23 what kind of compound was it?

24 A. ABT-594 was thought to act through neuronal

25 nicotinic receptors.

1 Q. NNRs, have you heard reference to that
2 terminology?

3 A. Yes.

4 Q. Am I correct that 594 was thought to be a member
5 of a -- perhaps a new class of analgesics?

6 A. Yes.

7 Q. And analgesics are pain relievers; is that
8 right?

9 A. Yes.

10 Q. So what Abbott was doing was looking at what
11 they thought might be a compound that would
12 introduce a new class of pain relievers to the
13 market; is that fair to say?

14 A. Yes.

15 Q. Were there other NNR products that Abbott was
16 investigating at the same time it was looking at
17 594?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: Yes.

20 BY MR. DAVIS:

21 Q. Do you know how many?

22 A. I don't know.

23 Q. Did any of them ever have ABT prefixed numbers
24 within the Abbott system, to your knowledge?

25 A. I don't know.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Have you ever heard of a compound named ABT-894?

2 A. I don't remember that compound.

3 Q. And you made reference earlier on to

4 pharmacokinetics. What are those? What is

5 pharmacokinetics?

6 A. Pharmacokinetics is the analysis of drug levels

7 in tissues or fluids.

8 Q. What does that tell you? Why is it important?

9 MR. PHILLIPS: Objection to the extent

10 you are seeking expert testimony.

11 BY MR. DAVIS:

12 Q. You are a neurologist?

13 A. Yes.

14 MR. PHILLIPS: But Dr. McCarthy is not

15 here as an expert witness. He's here as a

16 percipient witness.

17 MR. DAVIS: He's here to answer

18 whatever questions I wish to put to him, and the

19 court will determine whether he's competent to

20 offer various testimony within neurology.

21 MR. PHILLIPS: That's actually not

22 correct, Mr. Davis. That is not correct that

23 he's here to answer any questions you put to

24 him, as you well know.

25 MR. DAVIS: I'm certainly going to

1 area of research.

2 Q. Is he a doctor?

3 A. Ph.D.

4 Q. Does he still work at Abbott, to your knowledge?

5 A. I don't know.

6 Q. When is the last time you had any communication

7 with Mike Meyer?

8 A. I don't remember.

9 Q. If you'd take a look, please, at -- you'll see

10 that all of these documents are what we call

11 Bates stamped, meaning that there is a unique

12 identification number stamped on them.

13 If you take a look at the page of this

14 document -- actually, page 14, but it's Bates

15 stamped with a number that ends 5354. Do you

16 have that page in front of you?

17 A. Yes.

18 Q. It says here that:

19 The team believes ADT-594's

20 probability of registration is less

21 than average - it is first of a

22 class, and has emesis problems.

23 Do you see that?

24 A. Yes.

25 Q. Were you a member of some sort of team with

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 respect to the development of 594?

2 A. Yes.

3 Q. What was the team?

4 A. I believe it was called the ABT-594 development
5 team.

6 Q. What were the responsibilities of the team? I

7 apologize, some of these are basic, but somebody
8 has to tell us at some point in time.

9 A. To develop plans and operationalize those plans
10 in such a way that information is obtained about
11 the drug over time enabling decisions to move
12 forward with the drug development program until
13 either development stops or the drug is filed
14 for approval.

15 Q. You mentioned earlier that you worked in two
16 ventures when you were at Abbott, the analgesia
17 venture and also a psychopharmacology venture;
18 is that correct?

19 A. Yes.

20 Q. Did you work in those simultaneously or were
21 those in succession?

22 A. In succession.

23 Q. When you first went to work for Abbott, you were
24 working in the analgesia venture; is that right?

25 A. I think I was in the psychopharmacology venture

1 to start.

2 Q. And then you moved to the analgesia venture?

3 A. I think so.

4 Q. Were you in the analgesia venture when you left

5 Abbott?

6 A. No.

7 Q. What were you doing? What venture were you in

8 when you left Abbott?

9 A. The terminology had changed. The terminology

10 had changed. It was called something like

11 neuroscience development or --

12 Q. Can you take a moment and explain to me, how was

13 Abbott -- the portion of Abbott that you worked

14 in, the portion that helped sort of investigate

15 and develop compounds, how was it organized when

16 you first started working there?

17 A. There were venture teams that effectively

18 represented matrix teams of different functional

19 lines that came together to form a team and

20 develop the drug.

21 Q. Were the teams organized around particular

22 compounds?

23 A. Yes.

24 Q. So you were on the 594 team; is that right?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Were there teams for other compounds within

2 Abbott at the same time?

3 A. Yes.

4 Q. Were you on more than one team at any point in

5 time?

6 A. Yes.

7 Q. How many teams were you on at any point in time?

8 A. I don't remember.

9 Q. Were you the head of the 594 team?

10 A. No.

11 Q. Who was the head of the 594 team?

12 A. Chris Silber.

13 Q. He was also venture head?

14 A. Yes.

15 Q. Was he the head of each and every team within

16 the analgesia venture?

17 MR. PHILLIPS: Objection.

18 THE WITNESS: I don't know.

19 BY MR. DAVIS:

20 Q. Was he the head of other teams within that

21 venture?

22 A. Yes.

23 Q. Do you know how many other teams were in the

24 analgesia venture?

25 A. I don't remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Going back to Exhibit 1, the page that we were
2 referring to, does this accurately reflect sort
3 of the team's thinking as of July 1998, as best
4 you recall?

5 MR. PHILLIPS: Objection.

6 THE WITNESS: I don't remember.

7 BY MR. DAVIS:

8 Q. Do you recall discussions within Abbott about
9 the probability of registration for 594?

10 MR. PHILLIPS: Objection.

11 THE WITNESS: I remember -- yes.

12 BY MR. DAVIS:

13 Q. And by registration, you mean registration with
14 the FDA?

15 A. Yes.

16 Q. Does that mean getting the FDA to approve the
17 compound for distribution commercially?

18 A. Yes.

19 Q. What do you recall about the discussions within
20 Abbott about the probability of registration of
21 594?

22 A. I don't remember.

23 Q. Do you recall discussions about 594's emesis
24 problems?

25 A. Yes.

1 MR. PHILLIPS: Objection.

2 BY MR. DAVIS:

3 Q. What did you understand to be 594's emesis
4 problems?

5 A. By the end of 2001, that the emesis problems
6 outweighed the benefit of the drug.

7 Q. This document is dated from 1998. Is it fair to
8 say that you and others within Abbott were aware
9 of emesis problems associated with 594 at least
10 as of 1998?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: Yes.

13 MR. PHILLIPS: I'm sorry, Dr. McCarthy,
14 if you could pause very briefly so that if I
15 need to object, I can get my objection in.

16 THE WITNESS: Okay.

17 MR. PHILLIPS: Thank you.

18 BY MR. DAVIS:

19 Q. And I'm not trying to mislead you. No decision
20 had been made at that point as to whether or not
21 the usefulness of the drug outweighed the emesis
22 problems; is that right?

23 A. Yes.

24 Q. That was something that you were looking into;
25 correct?

1 A. Yes.

2 Q. But you knew, at least as of 1998, that there
3 were emesis/vomiting issues associated with this
4 particular compound?

5 A. Yes.

6 Q. If you could turn to the page that's Bates
7 number ends 5366. It's page 26 of the
8 presentation. The page is titled:

9 We considered three options
10 for A-173259; two backup strategies
11 and a parallel development strategy.

12 Do you see that?

13 A. Yes.

14 Q. While you were investigating 594, was your
15 group, the analgesia venture, also looking at
16 other potential backups for 594?

17 A. Yes.

18 Q. By backups, what does that mean?

19 A. Other drugs that could be put into development
20 at a future time or concurrently with a lead
21 candidate drug.

22 Q. Is it fair to say the backups are there so that
23 they can be development, further developed in
24 the event that the lead drug fails?

25 MR. PHILLIPS: Objection.

1 A. I believe so.

2 Q. Who is Grace Dunn?

3 A. Grace Dunn was at some point John Leonard's

4 administrative assistant.

5 Q. To your knowledge, did Chris Silber report to

6 John Leonard at this point in time?

7 A. I believe so.

8 Q. If you take a look at the third page of this

9 document, the one that's Bates number ends 5029,

10 do you see a reference to you?

11 A. Yes.

12 Q. The second paragraph says:

13 Bruce continued with a

14 discussion of the ABT-259 development

15 strategy.

16 Let's stop there. Is that the same

17 compound referenced in Exhibit 1?

18 A. Yes.

19 Q. And it says:

20 The criteria for switching

21 from ABT-594 to ABT-259 reside in a

22 clinically meaningful improvement in

23 GI side effects coupled with

24 comparable or superior efficacy to

25 that of ABT-594.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Is that consistent with your

2 understanding at that point in time?

3 A. Yes.

4 Q. And did you understand at that point in time

5 that 594 had something less than desirable GI

6 side effects?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: No.

9 BY MR. DAVIS:

10 Q. You didn't? When you make reference to

11 ABT-59 -- I'm sorry, ABT-259 having a meaningful

12 improvement -- strike that. Let me go back.

13 Did you understand as of this point in

14 time, early 1999, that ABT-594 had GI side

15 effects?

16 MR. PHILLIPS: Objection.

17 THE WITNESS: Can you repeat the

18 question?

19 BY MR. DAVIS:

20 Q. Certainly. Did you understand in early 1999

21 that ABT-594 had GI side effects?

22 A. Yes.

23 Q. And by GI side effects, we mean

24 gastrointestinal; correct?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. What GI side effects did you understand at that
2 point in time 594 had?

3 A. Nausea and vomiting.

4 Q. Did you regard that as desirable in a compound
5 like 594?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: No.

8 BY MR. DAVIS:

9 Q. And is it fair to say that what you were doing,
10 at least talking about in the course of this
11 meeting, was trying -- comparing 594 to another
12 compound, and that compound being 259, and you
13 were trying to determine whether 259 might be as
14 efficacious but not have the same side effects?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: I don't remember the
17 specific meeting.

18 BY MR. DAVIS:

19 Q. Do you recall generally that one of the reasons
20 why you were investigating 259 was because you
21 believed that it might have a better GI side
22 effect profile than 594?

23 A. Yes.

24 Q. Again, that is something you regarded as
25 desirable; correct?

1 A. Yes.

2 (Marked for identification

3 Deposition Exhibit No. 3.)

4 BY MR. DAVIS:

5 Q. Dr. McCarthy, you have what has been marked as

6 Exhibit 3. Is this a letter that you wrote to

7 Michael McCarthy in or about March of '99?

8 MR. PHILLIPS: I believe you misspoke.

9 Michael Meyer.

10 MR. DAVIS: I'm sorry. I apologize.

11 BY MR. DAVIS:

12 Q. Is this a letter that you wrote to Michael Meyer

13 on or about March of 1999?

14 A. I don't remember the letter.

15 Q. Is that your signature on the first page?

16 A. Yes.

17 Q. In the middle of the letter, let me just direct

18 your attention to the paragraph that begins:

19 Please note that we will not

20 be discussing the specific results of

21 the molar extraction trial.

22 Do you see that?

23 A. Yes.

24 Q. And is this reference to a trial of 594 that was

25 conducted involving trying to address pain in

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 the aftermath of having teeth removed?

2 A. Yes.

3 Q. Did Abbott actually conduct such a trial?

4 A. Yes.

5 Q. And it was a phase I trial; correct?

6 A. Phase II. Oh, phase I, I apologize.

7 Q. And did you participate in that trial in any

8 way?

9 A. In any way, yes.

10 Q. How so?

11 A. I was involved in interpretation of results

12 after study completion.

13 Q. Did that trial tell you anything about the

14 tolerability of 594?

15 A. Yes.

16 Q. What did you learn about the tolerability of 594

17 from that trial?

18 A. I don't remember specifics.

19 Q. Do you recall generally?

20 A. Again, observation of, at higher doses, nausea

21 and vomiting.

22 Q. And in the middle paragraph of this letter you

23 say:

24 I believe the advisors may

25 focus unnecessarily on ABT-594's

1 performance in the molar extraction

2 trial.

3 Do you recall what you mean by that?

4 A. No.

5 Q. And then if you look at the next page of this

6 document, it says:

7 Status and future of

8 ABT-594.

9 Do you see that?

10 A. Yes.

11 Q. And under phase I, the last sentence makes

12 reference to the maximally tolerated dose. What

13 is that?

14 MR. PHILLIPS: Sorry, Counsel. I think

15 it's the second to the last sentence.

16 BY MR. DAVIS:

17 Q. Do you see the sentence that states the

18 maximally tolerated dose?

19 A. Yes.

20 Q. What is the maximally tolerated dose?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: The maximally tolerated

23 dose here is reported as somewhere slightly

24 above 100 micrograms for fasted patients and 150

25 micrograms for fed patients.

1 BY MR. DAVIS:

2 Q. What does it mean when you reference a maximally

3 tolerated dose?

4 A. Maximally tolerated dose generally means the

5 dose at which -- above which most patients will

6 no longer tolerate the medication.

7 Q. Meaning that -- meaning what?

8 A. That the maximally tolerated dose suggests in

9 the experimental paradigm that doses above that

10 point are too poorly tolerated.

11 Q. When you say too poorly tolerated, specifically

12 what happens?

13 MR. PHILLIPS: Objection.

14 BY MR. DAVIS:

15 Q. What happened in 594?

16 A. I don't remember the specific reaction rates at

17 these doses or this maximally tolerated dose.

18 Q. Is it fair to say that above the maximally

19 tolerated dose, you get adverse events?

20 A. Yes.

21 Q. And that the adverse events are such that you

22 don't think the patients will or should take the

23 drug any further?

24 MR. PHILLIPS: Objection.

25 THE WITNESS: Yes.

1 (Marked for identification

2 Deposition Exhibit No. 4.)

3 BY MR. DAVIS:

4 Q. Dr. McCarthy, you have what has been marked as

5 Exhibit 4. I'll just ask you to look at this

6 document for a moment and tell me if you can

7 identify it for me.

8 A. The first page appears to be an e-mail sent by

9 Ritu A Lal, and the next page appears to be a

10 comparison of the probability of vomiting

11 against dose and AUC for two drugs, ABT-594 and

12 ABT-259, followed by a series of e-mails.

13 Q. Just focusing on the first two pages for a

14 moment, who is Ritu A Lal?

15 A. I don't remember.

16 Q. You recall, however, that one of the things that

17 you were looking at carefully with respect to

18 594 and its development was the propensity of

19 that compound perhaps to cause vomiting among

20 patients?

21 A. Yes.

22 Q. Is that because you believed that if the product

23 did cause undue amount of vomiting, that it

24 would affect the commercial viability of the

25 product, among other things?

1 MR. PHILLIPS: Objection.

2 THE WITNESS: Yes.

3 (Marked for identification

4 Deposition Exhibit No. 5.)

5 BY MR. DAVIS:

6 Q. Dr. McCarthy, I'd ask you to look briefly at

7 Exhibit 5, and tell me if you recognize this

8 presentation.

9 A. In general I do, yes.

10 Q. Earlier in your deposition today in Exhibit 2 we

11 made reference to an executive summary of an

12 analgesia venture portfolio review in January of

13 '99. Are these the slides from that review?

14 A. I don't know.

15 Q. Did you participate in the creation of these

16 slides?

17 A. I don't know if I participated in the creation

18 of these particular slides.

19 Q. On occasion did you help assemble slide

20 presentations concerning 594?

21 A. Yes.

22 Q. Were you required, on occasion, within Abbott to

23 make presentations about the status of 594 to

24 superiors within Abbott?

25 A. Yes.

1 A. Yes.

2 Q. If you turn to the page of this document that's

3 Bates numbered ended in 4978, there is a slide

4 there entitled:

5 Molar Extraction Study,

6 Preliminary Findings.

7 Would you just take a quick look at

8 that and tell me if you believe that this

9 accurately summarizes preliminary findings from

10 that molar extraction study?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: Yes.

13 BY MR. DAVIS:

14 Q. Would you turn to the page that's Bates number

15 ends in 5012. It's very near the end of the

16 presentation, about ten pages or so right from

17 the end.

18 MR. PHILLIPS: 12?

19 MR. DAVIS: 12, correct.

20 BY MR. DAVIS:

21 Q. Do you have that page in front of you?

22 A. Yes.

23 Q. This slide is titled:

24 ABT-594 Follow-on Strategy.

25 What is a follow-on strategy?

1 A. A follow-on strategy, follow-on refers to
2 compounds at earlier stages of development or
3 research that could continue in development, and
4 if the lead compound is discontinued, could
5 replace the lead compound.

6 So the strategy would define in what
7 ways decisions would be made to develop the
8 follow-ons.

9 Q. Is follow-on similar to or the same as backup?

10 A. Yes.

11 Q. Is it fair to say that in developing ABT-594 at
12 Abbott, one of the things that Abbott was
13 looking at was whether there were other similar
14 compounds that might have the same efficacy or
15 similar efficacy, but not necessarily the same
16 liabilities or side effects?

17 MR. PHILLIPS: Objection.

18 THE WITNESS: Yes.

19 BY MR. DAVIS:

20 Q. There is more than one NNR; correct?

21 A. Can you repeat that?

22 Q. To your knowledge, there was more than one NNR
23 compound; correct?

24 A. Yes.

25 Q. You could have different variations of the same

1 molecules; is that right?

2 A. Yes.

3 Q. And one of the things you were looking at was
4 whether different molecules within the NNR
5 family that might be -- one might be better than
6 another for purposes of commercializing a
7 compound?

8 MR. PHILLIPS: Objection.

9 THE WITNESS: Can you say that again?

10 BY MR. DAVIS:

11 Q. Certainly. That was a bad question.

12 Is it fair to say that when you were
13 working on 594, one of the things you were
14 looking at was comparing various compounds
15 within the NNR family to determine whether some
16 might be more attractive or have a higher
17 probability of success commercially than others?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: No.

20 BY MR. DAVIS:

21 Q. How was I incorrect?

22 A. Employees at Abbott were investigating whether
23 they could discover follow-ons that had the same
24 or better efficacy profile in preclinical models
25 with improved emetic profiles in preclinical

1 profiles.

2 Q. So it didn't extend necessarily all the way to
3 commercial viability, you were just looking to
4 determine whether they were similarly
5 efficacious compounds that didn't cause the same
6 degree of nausea or vomiting?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: No.

9 BY MR. DAVIS:

10 Q. You were looking at other compounds to determine
11 whether you could find similarly or more
12 efficacious compounds that didn't cause the same
13 degree of vomiting?

14 A. Yes.

15 Q. I hit it.

16 Actually, Dr. McCarthy, that question
17 brings me to one of the questions that we
18 non-technical types always have to ask, which is
19 the difference between nausea and vomiting; for
20 purposes of developing a compound like this,
21 what is it?

22 A. In humans nausea is a reported symptom, an
23 internal feeling reported by a patient or
24 subject; whereas vomiting is reported by the
25 subject as a physical manifestation of a defined

1 reflex in which the gastric contents are

2 expunged.

3 Q. Okay. Is it fair to say that vomiting -- I

4 think we know what vomiting is. We've probably

5 all had that pleasure. Is it fair to say that

6 nausea is not ill, but going to be, or perhaps

7 going to be?

8 A. No.

9 Q. Nausea is the feeling that you may vomit; is

10 that fair to say?

11 A. I think that's incomplete.

12 Q. How is it incomplete?

13 A. Nausea is not necessarily associated with

14 vomiting.

15 Q. How is it described for clinical purposes, as

16 best you know, nausea?

17 A. A queasy feeling, often associated with a sense

18 of upset senses referenced to the abdominal

19 area.

20 Q. Thank you.

21 (Marked for identification

22 Deposition Exhibit No. 6.)

23 BY MR. DAVIS:

24 Q. Would you look, please, at Exhibit 6 for a

25 moment, and tell me if you've seen this document

1 before.

2 MR. DAVIS: And actually, I'll just
3 note for the record, this came to us in this
4 form. This may be more than one document,
5 because there seems to be a title page at the
6 page Bates number ended in 8986 and then another
7 title page at Bates number ended in 9000.

8 MR. PHILLIPS: Mr. Davis, when you say
9 came to you in this form, you mean it was
10 clipped?

11 MR. DAVIS: I believe it all came as a
12 single document.

13 MR. PHILLIPS: In clipped form or --

14 MR. DAVIS: I don't know if it was
15 clipped or stapled or the like.

16 MR. PHILLIPS: Okay. Thank you.

17 THE WITNESS: I generally recognize
18 this type of document. I don't remember this
19 one in particular.

20 BY MR. DAVIS:

21 Q. When you were at Abbott, did you participate in
22 the creation of development plans for 594?

23 A. Yes.

24 Q. As you sit here today, do you believe that you
25 played any role in the creation of this

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 development plan for 594?

2 A. I may have.

3 Q. What portion would you have played a role in

4 developing or creating?

5 A. I may have played a portion in section A.

6 Q. What page are you looking at?

7 A. The table of contents.

8 Q. And the Bates number in the lower right-hand

9 corner?

10 A. Bates number 19001.

11 Q. Thank you. I'm sorry, what sections do you

12 think you may have contributed to?

13 A. Section A.

14 Q. Background and rationale. Anything else?

15 A. I may have participated also on the preparation

16 of section D.

17 Q. Clinical trial program?

18 A. Yes. And may have aided or assisted in the

19 review of other sections.

20 Q. Who was responsible within Abbott for putting

21 together the development plans like this for

22 594?

23 A. In general, it was a team effort with an

24 operations manager taking on responsibility for

25 compiling the different contributions.

1 Q. Is it fair to say that there was someone
2 responsible for organizing the effort? That
3 would be the operations manager; right?

4 A. Yes.

5 Q. But the actual substance of the development plan
6 would come from various members of the team?

7 A. That's correct.

8 Q. Including you?

9 A. Yes.

10 Q. Would you review the entire report before it was
11 submitted?

12 A. It depended on when.

13 Q. For what purpose were the development plans
14 created?

15 A. For the team itself to have a central source for
16 its plans and for communicating the plans of the
17 team to other parts of -- other employees and
18 teams in the organization.

19 Q. You anticipated my next question, which is to
20 whom were they submitted.

21 A. I don't know.

22 Q. Were they submitted to higher-ups in the Abbott
23 hierarchy?

24 MR. PHILLIPS: Objection.

25 THE WITNESS: I believe they were

1 THE WITNESS: Not that I'm aware of.

2 BY MR. DAVIS:

3 Q. Was the information contained in the development

4 plans, to the best of your knowledge, reasonably

5 accurate at the time the plan was created?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: I don't know.

8 BY MR. DAVIS:

9 Q. Was that your goal to try to include what you

10 understood to be accurate information?

11 A. It would have been my goal to include accurate

12 information, yes.

13 Q. Is it your belief that that was the goal of

14 others who participated in the development plan

15 creation process as well?

16 A. I would be speculating.

17 (Marked for identification

18 Deposition Exhibit No. 7.)

19 BY MR. DAVIS:

20 Q. Dr. McCarthy, would you look at this document

21 for a moment and tell me, if you can, what is

22 the pharmaceutical discovery internal review?

23 A. I don't remember specifically.

24 Q. Would you turn, please, to the third page of

25 this document, the Bates number ends in 4178,

1 reviewing in an oversight or editorial mode, no.

2 Q. Was Dr. Meyer a member of the 594 project team?

3 A. Yes.

4 Q. What was his responsibility?

5 A. His responsibility was in -- as a team leader in

6 discovery or research to support ongoing

7 preclinical studies with 594, and I believe as

8 well to identify or discover new compounds, as

9 well as on the 594 team to provide a link to the

10 research organization.

11 Q. Was there a project underway at Abbott in 1999

12 to identify a follow-on to ABT-594?

13 A. I don't remember.

14 Q. Did you play any role in the project to identify

15 follow-ons or backups for 594?

16 MR. PHILLIPS: Objection.

17 THE WITNESS: I did not play a role in

18 the effort to identify follow-ons, which is a

19 preclinical research discovery effort.

20 BY MR. DAVIS:

21 Q. There is a reference here to DDC. Do you know

22 what that is?

23 A. I can't remember what it stands for.

24 Q. On project leader in the upper left-hand corner,

25 it says Michael Meyer. Under biology it says

1 A. I don't think so.

2 Q. As you sit here today, do you have any further
3 recollection of what team neuro was?

4 A. The only recollection I have of team neuro was
5 early on in my time at Abbott, I and other
6 employees working in the neuroscience area at
7 Abbott, including discovery and development and
8 commercial, attempted to essentially brand
9 within Abbott the partnership between research,
10 clinical and commercial as a team neuro, as a
11 description for the entire group to pull people
12 together.

13 Q. Did that catch on?

14 A. No.

15 Q. Good try.

16 (Marked for identification
17 Deposition Exhibit No. 10.)

18 BY MR. DAVIS:

19 Q. Dr. McCarthy, you have in front of you what's
20 been marked as Exhibit 10. Let me ask you to
21 look at the document for a moment and tell me
22 first whether you recall seeing documents in
23 this format at Abbott.

24 A. I believe so, yes.

25 Q. What is this?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. Well, it says it's a project status report.

2 Q. Did you participate in the creation of project

3 status reports for ABT-594 while you were

4 working on that particular compound?

5 A. I don't remember.

6 Q. Do you know who within the company was

7 responsible for coming up with monthly status

8 reports, project status reports, for ABT-594?

9 A. I believe the operations manager would have

10 created these.

11 Q. Who was the operations manager on 594?

12 A. I believe at successive times there were Olga

13 Jasinsky and Mike Biarnesen.

14 (Discussion held off the record.)

15 BY MR. DAVIS:

16 Q. Did Ms. Jasinsky precede Mr. Biarnesen as

17 operations manager?

18 A. Yes.

19 Q. Is Mr. Biarnesen still employed at Abbott, to

20 your knowledge?

21 A. I don't know.

22 Q. Why was it that Mr. Biarnesen succeeded Ms.

23 Jasinsky?

24 A. Olga Jasinsky took another position in the

25 development organization.

1 before the clinical studies begin?

2 MR. PHILLIPS: Objection.

3 THE WITNESS: Clinical -- in order to

4 start clinical trials in general, protocols are

5 sent. If done in the United States, a sponsor

6 does submit clinical trial protocols.

7 BY MR. DAVIS:

8 Q. To the FDA?

9 A. In advance of starting a study, yes.

10 Q. On the 114 trial, where was that trial

11 conducted?

12 A. In the United States.

13 Q. Only at various sites exclusively in the U.S.?

14 A. I believe so, yes.

15 Q. Did you participate in the creation of the

16 protocol for 114?

17 A. Yes.

18 Q. What role did you play?

19 A. The oversight of the design of the study.

20 Q. Had you previously designed clinical trials?

21 A. Yes.

22 Q. Where did you get your education in designing

23 clinical trials?

24 A. At Abbott, on-the-job training.

25 Q. How many prior clinical trials had you created?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. I don't remember. I don't remember.

2 Q. Do you recall that the 114 clinical trial called
3 for 320 subjects?

4 MR. PHILLIPS: Objection.

5 THE WITNESS: I don't remember.

6 BY MR. DAVIS:

7 Q. How do you go about determining how many
8 subjects you need for a particular clinical
9 trial?

10 A. Predominantly in discussions with statisticians
11 an estimate is made on how large a treatment
12 effect is anticipated, and the statisticians
13 help the team determine how many patients would
14 be needed in a study to discern that treatment
15 difference from the comparator.

16 Q. What is your understanding of the effect on a
17 clinical trial if the target number of subjects
18 is not reached?

19 MR. PHILLIPS: Objection.

20 THE WITNESS: Can you restate the
21 question?

22 BY MR. DAVIS:

23 Q. Yes. What is your understanding of the effect
24 on a clinical trial if, in the course of the
25 trial, the predetermined number of target

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 subjects is not in fact reached?

2 MR. PHILLIPS: Objection.

3 THE WITNESS: Well, the study would end

4 with fewer patients. It would likely end

5 earlier than it would have otherwise if it went

6 to the end.

7 BY MR. DAVIS:

8 Q. Does not reaching the targeted number of

9 subjects in a trial affect the statistical

10 validity of the trial in any way?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: I think I would be

13 speculating.

14 BY MR. DAVIS:

15 Q. You don't know one way or the other?

16 A. Yeah, I don't know.

17 Q. Does it affect the usefulness of the trial for

18 purposes of determining whether to move on to

19 the next phase of the study?

20 MR. PHILLIPS: Objection.

21 THE WITNESS: I don't think so.

22 BY MR. DAVIS:

23 Q. Have you heard the term premature terminations

24 or premature -- let's start with premature

25 terminations.

1 A. Yes.

2 Q. What is a premature termination?

3 A. A patient who exits the study before the final

4 study -- the planned final study point.

5 Q. Do premature terminations in the course of a

6 clinical trial affect the enrollment of the

7 clinical trial?

8 MR. PHILLIPS: Objection.

9 THE WITNESS: Only if an individual

10 investigator is making a decision to not enroll

11 the next patient based on experiences they have

12 had with prior patients enrolled in the study.

13 BY MR. DAVIS:

14 Q. Further down on the same page of Exhibit 10,

15 there is a reference to a 114 neuropathic pain

16 investigator meeting. Do you see that? It's

17 still under progress gauges.

18 A. Yes, I do.

19 Q. Did you participate in that meeting?

20 A. I believe I did.

21 Q. What is the purpose of the investigator meeting?

22 A. The investigator meeting is held to train all of

23 the investigators who will be performing the

24 study.

25 Q. Are there materials given to the investigators

1 in the course of a meeting?

2 A. Yes.

3 Q. What materials?

4 A. They include -- generally include the protocol

5 and other instructions on how to work

6 effectively with the sponsor during the course

7 of the study.

8 Q. Were copies of those materials retained by

9 Abbott, to your knowledge?

10 A. I don't know.

11 (Marked for identification

12 Deposition Exhibit No. 11.)

13 BY MR. DAVIS:

14 Q. Dr. McCarthy, I'll show you what appears to be

15 another project status report for 594 from

16 April 2000. Do you recall seeing this document?

17 A. I don't.

18 Q. If you would look at the bottom, near the bottom

19 of the first page, it says under current month:

20 First patient enrolled phase

21 IIb 425.

22 Do you see that?

23 A. Uh-huh.

24 Q. Now, phase IIb, that was the -- the 114 trial

25 was a phase IIb study; correct?

1 A. Yes.

2 Q. What is the difference between a phase IIa study

3 and a phase IIb study?

4 A. In a phase IIb study, its objective generally

5 includes dose ranging.

6 Q. And that's not generally an objective of a phase

7 IIa study?

8 A. Yes.

9 Q. Was one of the objectives of the 114 study to

10 determine appropriate dosing for 594 in human

11 patients?

12 A. Yes.

13 Q. Was that achieved?

14 A. Yes.

15 Q. Did you determine what the appropriate dose

16 would be?

17 A. No.

18 Q. Why not?

19 A. Because ultimately there was no dose for which

20 the tolerability profile outweighed the benefits

21 of the efficacy.

22 Q. Is this -- you see the date of April 25th. Is

23 that consistent with your general recollection

24 of when patients were first enrolled in the 114

25 study?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 May 2000. Of these three to five
2 compounds, one will be chosen in July
3 slash August for fourth quarter 2000
4 DDC.

5 Do you see that?

6 A. Yes.

7 Q. You don't have any recollection of what DDC is?

8 A. I don't remember what the acronym stands for.

9 Q. Do you know what the DDC was, even if you don't
10 recall the acronym?

11 A. The DDC was a meeting in which the research or
12 discovery organization presented to its
13 management the culmination of their work on
14 identifying a new compound. After that meeting,
15 if the management approved the compound moving
16 forward, it would move into development.

17 Q. Did you think that it was a smart strategy for
18 Abbott to be identifying follow-on compounds for
19 594 as of, you know, mid 2000?

20 MR. PHILLIPS: Objection.

21 THE WITNESS: I can't be specific about
22 mid 2000, but in general, I think I thought it
23 was a smart strategy to be identifying
24 follow-ons.

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Is that because you believed that tolerability
2 problems that had been observed with 594
3 ultimately might not be resolved?

4 A. No.

5 Q. Why?

6 A. I thought it was useful because, once we knew
7 that the drug had efficacy in pain, because it
8 was a first-in-class or we had demonstrated that
9 a new class of drugs could be analgesic, drugs
10 at that early stage fail for a variety of
11 reasons and fail very often, so it is the most
12 sensible development strategy for a company to
13 have multiple follow-ons for their lead
14 compound.

15 Q. Did Abbott conduct any clinical trials for 594,
16 in whole or in part, to gain information about
17 NNRs generally, as opposed to 594 specifically?

18 A. Yes.

19 Q. That was one of Abbott's purposes in running 594
20 trials?

21 A. Yes.

22 Q. Was that one of the purposes for running the 114
23 trial?

24 A. No.

25 Q. Abbott was not running the 114 trial to try and

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 get more information about NNRs generally?

2 A. No.

3 MR. PHILLIPS: Counsel, at a convenient

4 point, I'd like to take a short break.

5 MR. DAVIS: We can do it now.

6 (A brief recess was taken.)

7 (Marked for identification

8 Deposition Exhibit No. 12.)

9 BY MR. DAVIS:

10 Q. Dr. McCarthy, you have Exhibit Number 12 in

11 front of you. I want to ask you to look at that

12 document for a moment and tell me whether you

13 recognize it.

14 A. I don't recognize the document in total. I do

15 recognize some slides, in particular the

16 clinical results slides, as appearing like the

17 slides we often used in describing the results

18 of the clinical trials.

19 Q. Do you recall participating in a presentation in

20 May of 2000 addressing 594, in part?

21 A. No.

22 Q. Would you look, please, at page 12 of the

23 slides. It's the one that Bates' number ends in

24 1828. Do you have that page?

25 A. Yes.

1 Q. The page is titled:

2 Phase IIb Trial in Diabetic

3 Neuropathy.

4 Do you see that?

5 A. Yes.

6 Q. This is the 114 trial?

7 A. Yes.

8 Q. Does this accurately reflect the study design,

9 for example, of that trial?

10 A. I believe so.

11 Q. It mentions four groups with different dosing

12 levels; correct?

13 A. Yes.

14 Q. One of the groups receiving a placebo; correct?

15 A. Yes.

16 Q. So is it fair to say that the 114 trial was

17 testing patients on placebo, plus three

18 different dosing levels?

19 A. I would phrase it that there were three

20 different dose levels and placebo tested.

21 Q. Were the patients to be distributed roughly

22 equally among the three different dosing levels?

23 A. Yes.

24 Q. And among placebo?

25 A. Sorry. Equally distributed amongst all four

1 groups.

2 Q. So at the end of the day, at the end of the

3 trial, you would expect that patients who had

4 enrolled in the trial would be distributed

5 roughly 25 percent in each of those categories;

6 is that right?

7 A. Yes.

8 Q. And it says in the bottom:

9 Results expected by

10 January 2001.

11 What results were expected by

12 January 2001?

13 A. I don't know.

14 Q. Did you understand as of roughly May 2000 that

15 the results of the 114 study would be unblinded

16 and available for examination by January of

17 2001?

18 A. I don't remember.

19 Q. Do you recall that the study length was changed

20 at some point in time?

21 A. I believe it was.

22 Q. Now, would you look at the next page of this

23 document, please, and there is a reference there

24 to discovery program update. Do you see that?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 generally made funding decisions of that type
2 within your group?

3 MR. PHILLIPS: Objection.

4 THE WITNESS: Yes.

5 BY MR. DAVIS:

6 Q. Dr. McCarthy, just briefly, how frequently did
7 you interact with John Leonard when you worked
8 at Abbott?

9 A. I would say, on average, maybe once a month.

10 Q. Did you meet with him once a month to update him
11 on the status of the projects you were working
12 on?

13 A. No.

14 Q. In what context would you interact with him on a
15 once-a-month basis?

16 A. Group -- various group meetings.

17 Q. Did you ever inform John Leonard of the status
18 of the 114 study?

19 A. It's possible, yes.

20 Q. Do you have specific recollection of doing so at
21 any point in time?

22 A. Not specific, no.

23 Q. Do you believe that you did so?

24 A. It's likely.

25 (Marked for identification)

1 Deposition Exhibit No. 14.)

2 BY MR. DAVIS:

3 Q. Looking at Exhibit 14, this appears to be a 594

4 project status report for June of 2000. Under

5 the second bullet point from the top it says:

6 Enrollment in the 114 study

7 is slower than planned and is under

8 scrutiny by team personnel.

9 Do you see that?

10 A. Yes.

11 Q. Do you recall that there was, as of June or so

12 2000, a recognition within Abbott that the

13 enrollment in the 114 study was going slower

14 than planned?

15 A. Yes.

16 Q. Was that a cause of concern?

17 A. Yes.

18 Q. Why?

19 A. There's always concern in the organization when

20 enrollment targets are not being met because

21 that will translate into a delayed time to

22 information.

23 Q. Would it translate -- could it have any other

24 adverse impact on a clinical trial, to your

25 knowledge?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 MR. PHILLIPS: Objection.

2 THE WITNESS: No.

3 BY MR. DAVIS:

4 Q. Was there a preset amount of time within which
5 the enrollment was going to take place for the
6 114 study?

7 A. I believe there was.

8 Q. So if the enrollment was slow and you hadn't
9 enrolled enough patients or subjects in the
10 study by the time the study ended, could that
11 impact the results of the study?

12 MR. PHILLIPS: Objection.

13 THE WITNESS: Can you restate? Can you
14 say that again?

15 BY MR. DAVIS:

16 Q. If the enrollment in the 114 study was going
17 slower than planned such that you didn't enroll
18 the targeted number of subjects before the study
19 ended, could that impact the results of the
20 study?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: I'm getting confused with
23 the question.

24 BY MR. DAVIS:

25 Q. Can you identify for me what you find confusing?

1 A. The end of the study is -- the use of the term
2 end of the study, so if fewer patients are
3 enrolled -- whatever the last patient enrolled
4 is, whatever that amount is, is the end of the
5 study.

6 Q. Let's go back for a moment. In the initial
7 design of the 114 study, was there a specified
8 date on which enrollment would end?

9 A. No.

10 Q. So enrollment was expected to continue until the
11 subject -- number of subjects had been achieved?

12 A. Yes.

13 Q. Did you have an expectation as to when that
14 would occur?

15 A. Yes.

16 Q. Do you know what that date was?

17 A. I don't remember.

18 Q. Further down on Exhibit 14, under July
19 projections, it says:

20 Contact all 114
21 investigators to determine enrollment
22 obstacles.

23 Do you see that?

24 A. Yes.

25 Q. Did you play any role in that, performing that

1 task?

2 A. I don't remember specifically, but generally,

3 yes.

4 Q. Did you ever learn what enrollment obstacles the

5 investigators were facing?

6 A. I don't recollect the specific obstacles that we

7 concluded.

8 Q. The next bullet point says:

9 Review early terminations

10 and adverse event profile to

11 determine strategic options to

12 address slow enrollment.

13 Did I read that correctly?

14 A. Yes.

15 Q. How were the early terminations related to slow

16 enrollment?

17 A. We had the hypothesis that individual

18 investigators were less likely to enroll a new

19 patient into the trial based on their

20 experiences with patients who had left the trial

21 early due to adverse events.

22 Q. Also, there is a reference there to the adverse

23 event profile. Did you actually review the

24 adverse event profile for this trial 114 at or

25 around this time?

1 A. In a general way.

2 Q. What did you learn?

3 A. I don't recall what we specifically learned.

4 Q. Do you recall generally what you learned?

5 A. We learned that we continued to -- we learned

6 that we saw -- or we thought we were hearing of

7 nausea and vomiting again in this trial as we

8 had with previous trials.

9 Q. Did the amount of nausea and vomiting or the

10 rate of adverse events linked to nausea and

11 vomiting concern you in any way?

12 A. Concern me in any way? Yes.

13 Q. How so?

14 A. Concern for the interest of the investigator to

15 enroll a new patient into the study.

16 Q. Any other way?

17 A. No.

18 Q. Was the rate -- were the rate of adverse events

19 associated with nausea and vomiting greater

20 than, equal to or less than what you had

21 anticipated going into the trial?

22 A. I can't answer that because one can't calculate

23 the rate until the study finishes.

24 Q. Do you know what the rate of adverse events was

25 as of June 2000?

1 clinical issues, I believe so.

2 Q. And one of the weaknesses of 594 identified in
3 this plan is:

4 Adverse events (especially
5 nausea, vomiting and dizziness) may
6 limit realization of full efficacy.

7 Do you see that?

8 A. Yes.

9 Q. Let's go back for a moment. As the 114 trial
10 was progressing, you were getting reports of the
11 adverse events taking place in the trial;
12 correct?

13 A. Yes.

14 Q. And you didn't know precisely what compound had
15 been administered to the people who were
16 suffering the adverse events, but you knew the
17 nature of the adverse events; is that right?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: I knew the compound that
20 was being administered.

21 BY MR. DAVIS:

22 Q. Let me take a step back for a moment. When you
23 received information about an adverse event,
24 what information did you receive?

25 MR. PHILLIPS: Objection.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 THE WITNESS: Ultimately, we would
2 receive a case report form that describes the
3 adverse event, including date and time of onset,
4 duration, description of the event, and an
5 assessment of causality, meaning whether it was
6 related or not related to the study medication.

7 BY MR. DAVIS:

8 Q. So did you know, for example, in the 2000 that
9 patients were experiencing adverse events on
10 account of their ingestion of 594 in the study?

11 A. No.

12 Q. You knew that patients in the study were
13 receiving -- were suffering adverse events,
14 including nausea and vomiting; correct?

15 A. Yes.

16 Q. But you didn't know whether the particular
17 patients who were experiencing nausea and
18 vomiting had actually been administered 594; is
19 that right?

20 A. Yes.

21 Q. You also knew the rate of the adverse events;
22 correct?

23 A. No.

24 Q. So you didn't know how many of the people who
25 had enrolled in the study to that point in time

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 had suffered adverse events?

2 A. I don't remember that we calculated that rate

3 value.

4 Q. You could easily have done that, though, by

5 simply looking at the total number of people

6 enrolled and the total number of adverse events;

7 right?

8 A. No, it could not have been done easily.

9 Q. And you are not aware of anyone within Abbott

10 calculating adverse event rates while the study

11 was still underway?

12 MR. PHILLIPS: Objection.

13 THE WITNESS: No, I'm not aware.

14 BY MR. DAVIS:

15 Q. Dr. McCarthy, were you aware in or prior to

16 March of 2001 that Abbott had signed a research

17 funding agreement with John Hancock?

18 THE WITNESS: Can you repeat?

19 BY MR. DAVIS:

20 Q. Certainly. Were you aware in or before March of

21 2001 that Abbott and John Hancock had entered

22 into or were negotiating a research funding

23 agreement?

24 A. I can't remember when I was aware.

25 Q. Were you aware before you were asked to be

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 deposed in this case that Hancock and Abbott had
2 entered into a research funding agreement?

3 A. Yes.

4 Q. What is the earliest date that you can recall
5 being aware of the existence of that agreement?

6 A. I don't remember.

7 Q. Were you aware at any point in time during the
8 114 trial that Hancock and Abbott were
9 negotiating a research funding agreement?

10 A. I don't remember.

11 Q. Were you aware at any point in time while you
12 were working on the 114 trial that Abbott was
13 talking to Hancock about funding some or all of
14 the development of 594?

15 A. I don't remember.

16 Q. Are you able to recall any discussions within
17 Abbott whether funding for 594 or the
18 development of 594 would be affected in any way
19 by any deal with John Hancock?

20 A. No, I don't remember that.

21 (Marked for identification
22 Deposition Exhibit No. 18.)

23 BY MR. DAVIS:

24 Q. You have in front of you Exhibit 18, which is an
25 e-mail from Ms. Collicott to Dr. Silber with a

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 cc to you. Do you recall receiving this e-mail?

2 A. No.

3 Q. Do you recall that in August of 2000 a decision

4 was made to extend the enrollment deadline for

5 the 114 trial?

6 A. No, I don't remember at that time. I remember

7 generally that there were changes in the target

8 end date.

9 Q. If you take a look, please, at the -- if you

10 look at the letter that is attached to Ms.

11 Collicott's e-mail, the very first paragraph

12 says:

13 I am pleased to inform you

14 that the enrollment period for study

15 M99-114 has been extended.

16 What was the original enrollment period

17 for that study?

18 A. I don't remember.

19 Q. Do you recall that at some point in time the

20 enrollment period was extended?

21 A. Yes.

22 Q. Who made the decision to extend the enrollment

23 period?

24 A. I don't remember.

25 Q. Did you participate in that decision?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. I think I did.

2 Q. What role did you play?

3 A. I would have had a role in describing where we

4 thought the trial -- how long it would take,

5 what things we could do to speed enrollment or

6 get it back on track.

7 Q. Did you think that as of August 2000 enrollment

8 was, in fact, off track?

9 MR. PHILLIPS: Objection.

10 THE WITNESS: I believe so.

11 BY MR. DAVIS:

12 Q. Who else participated in the decision to extend

13 the enrollment period for the 114 trial?

14 A. I don't remember.

15 Q. Did Dr. Silber participate?

16 A. I can't remember.

17 Q. Did you have the authority at that point in time

18 to -- yourself to order that the enrollment

19 period be extended?

20 A. No, I don't think so.

21 Q. So you needed somebody above you to okay it?

22 A. Yes.

23 Q. It says:

24 The last day for

25 randomization will be March 2, 2001.

1 What is randomization?

2 A. Randomization is the point at which a patient
3 who has been screened for entry into the study
4 is assigned a randomized number, a treatment
5 assignment, and is the formal point of entry
6 into the study period for -- into the study for
7 a patient.

8 Q. Why was it that the decision was made to extend
9 the enrollment for this particular trial?

10 A. I believe it was because enrollment was going
11 slow, and in order to achieve the target number
12 of patients in the study, the enrollment period
13 was extended.

14 Q. What did you understand could or would happen if
15 you didn't reach the targeted number of subjects
16 or patients for the study?

17 A. There would be fewer patients in the study.

18 Q. Did you think that that would affect the study
19 in any way?

20 A. If there were fewer patients in the study than
21 planned, the outcome of the study would, no
22 matter what the number of patients, depend on
23 the treatment effect observed. And if the
24 treatment effect is smaller than what the sample
25 size of the study supports, you -- but it does

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 have a true effect, you may not be able to
2 demonstrate statistical significance versus
3 placebo.

4 Q. So it's fair to say that you understood, at
5 least as of August 2000, that if you didn't
6 reach 320 subjects, the target number of
7 subjects for the 114 study, that it could
8 affect -- could affect the statistical
9 significance of the trial?

10 MR. PHILLIPS: Objection.

11 THE WITNESS: No, I think the answer is
12 no to that.

13 BY MR. DAVIS:

14 Q. You understood that it could impact the
15 information that could be drawn from the trial;
16 is that right?

17 MR. PHILLIPS: Objection.

18 THE WITNESS: Yes.

19 BY MR. DAVIS:

20 Q. Did you regard it as undesirable to complete the
21 trial without having the appropriate number or
22 the target number of subjects?

23 MR. PHILLIPS: Objection.

24 THE WITNESS: No.

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. So you were extending enrollment so that you
2 could reach 320 subjects, but it really didn't
3 matter?

4 MR. PHILLIPS: Objection.

5 Argumentative.

6 BY MR. DAVIS:

7 Q. Is that what you are saying?

8 A. No.

9 Q. Then why did you take the step to extend the
10 enrollment period so that you could reach 320
11 subjects?

12 A. I don't think it was undesirable, but it was
13 less desirable.

14 Q. It would be less desirable not to reach the
15 target number of subjects; is that fair?

16 A. Yes.

17 Q. Less desirable why?

18 A. If the treatment effect is of a certain size,
19 the probability that the difference between drug
20 treatment and placebo was statistically
21 significantly different would be smaller.

22 Q. If you didn't reach the target number of
23 subjects, 320, did that create at least the risk
24 that you might have to redo that trial at some
25 later point in time?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 MR. PHILLIPS: Objection.

2 THE WITNESS: It would depend.

3 BY MR. DAVIS:

4 Q. I understand it would depend, but my question

5 is, did you understand that if you didn't reach

6 the 320 target subjects, that at least created

7 the risk that you might have to redo that trial?

8 A. Yes.

9 (Marked for identification

10 Deposition Exhibit No. 19.)

11 BY MR. DAVIS:

12 Q. Dr. McCarthy, I'll show you what has been marked

13 as Exhibit 19 and ask to you look at the

14 document for a moment and tell me if you believe

15 you've seen it before.

16 A. I don't recollect this specific document.

17 Q. You recall -- I think we saw in other documents

18 a few minutes ago that one of the things that

19 you and others on the 594 team did in response

20 to the slow enrollment in 114 was to consider

21 retaining some patient recruitment firms?

22 A. Yes.

23 Q. Was Phone Screen and GCI Healthcare Clinical

24 Trial Recruitment one of the firms that you

25 considered?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. I don't remember.

2 Q. Who within your organization was given

3 responsibility for soliciting proposals from

4 clinical patient recruitment firms?

5 A. I believe in part Marilyn Collicott would have

6 been involved.

7 Q. Did you play any role in that process, other

8 than tasking Ms. Collicott to obtain proposals?

9 A. I would have discussed with Marilyn her

10 findings.

11 Q. Did you meet with any of the proposed patient

12 recruitment firms or representatives of those

13 firms?

14 A. I don't remember.

15 Q. Now, if you take a look at the second page of

16 this document -- just going back to the first

17 page, it says it was developed for Abbott

18 Laboratory, September 28, 2000. Do you see

19 that?

20 A. Yes.

21 Q. Is that consistent with your recollection of the

22 approximate time frame within which you were

23 looking at patient recruitment firms for the 114

24 trial?

25 A. I think so.

1 Q. Did you understand in September of 2000 that the
2 114 trial had approximately a 34 percent dropout
3 rate?

4 A. I can't remember.

5 Q. 34 percent, that would be a higher percentage
6 than the number of patients in the trial you
7 would understand would receive placebo; correct?

8 A. Say that again.

9 MR. PHILLIPS: Objection.

10 BY MR. DAVIS:

11 Q. 34 percent was higher than the number of
12 subjects in the trial or the percentage of
13 subjects in the trial who you understood would
14 receive placebo; correct?

15 A. I'm sorry, I'm not understanding the question.

16 Q. I think we established earlier that the trial
17 was designed such that there would be four
18 possible doses or products delivered to
19 patients: Either placebo, or 594 in a 150
20 microgram dose or a 225 microgram dose or a 300
21 microgram dose; correct?

22 A. Yes.

23 Q. And you expected that the percentage of patients
24 receiving each one of those four possibilities
25 would be approximately 25 percent; correct?

1 A. Yes.

2 Q. So if you had a 34 percent dropout rate as of
3 September of 2000, you could at least determine
4 that some percentage of the patients who were
5 dropping out were receiving 594; correct?

6 A. I wouldn't know -- I would not know at that
7 point what the percentage of patients who
8 received 594 were. On average it would be 25
9 percent, but I wouldn't know what fraction of
10 patients had been randomized to each group.

11 Q. But you could -- just looking at the data at
12 that point in time, it would give you reason to
13 believe that patients who were receiving 594, in
14 addition to placebo, were dropping out of the
15 study; is that right?

16 MR. PHILLIPS: Objection.

17 THE WITNESS: I wouldn't know.

18 BY MR. DAVIS:

19 Q. The next section titled Key Enrollment
20 Challenges says:

21 While painful diabetic
22 neuropathy is a debilitating
23 condition that has a significant
24 impact on quality of life, study
25 sites are confronted with a number of

1 THE WITNESS: I don't remember.

2 BY MR. DAVIS:

3 Q. Did you believe that the tolerability problems
4 that you previously had observed with respect to
5 594 were playing any role in the adverse events
6 that you were observing in that trial?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: Yes.

9 BY MR. DAVIS:

10 Q. What role?

11 A. That they may be related.

12 (Discussion held off the record.)

13 (Lunch recess.)

14 BY MR. DAVIS:

15 Q. Before we get back into the documents, Dr.

16 McCarthy, when you left Abbott, did you sign any
17 severance agreements or consulting agreements
18 with them?

19 A. I believe I did, yes.

20 Q. And did that call for you to cooperate with
21 respect to testimony or the like in any matters?

22 A. I don't remember.

23 Q. Did you retain a copy of that agreement?

24 A. Yes.

25 Q. And who did you negotiate that agreement with at

1 A. I don't remember.

2 Q. Do you recall working with BBK?

3 A. No.

4 Q. Did BBK come up with an action plan for patient
5 recruitment for 114?

6 A. I don't remember.

7 (Marked for identification
8 Deposition Exhibit No. 21.)

9 BY MR. DAVIS:

10 Q. Dr. McCarthy, I show you what's been marked as
11 Exhibit 21, and ask if you've seen this document
12 before.

13 A. No, I don't think so.

14 Q. On its face, it appears to be another project
15 status report for the month of November 2000 for
16 ABT-594. The second bullet point down says:
17 Proposals and timelines from
18 three patient recruitment firms were
19 reviewed with a conclusion reached
20 that hiring a recruitment firm to
21 increase enrollment for study M99-114
22 was not a viable option at this time.

23 Is it consistent with your recollection
24 that Abbott decided in or around this time not
25 to retain a patient recruitment firm for the 114

1 study?

2 A. Yes, it is consistent.

3 Q. Who made the decision not to retain the patient

4 recruitment firm?

5 A. I don't remember.

6 Q. Did you participate in that decision?

7 A. I don't remember.

8 Q. Was the decision explained to you at the time?

9 A. I don't remember.

10 Q. Do you have any recollection as to why it was

11 that in or around November 2000 Abbott decided

12 not to hire a recruiting firm to increase

13 enrollment for the 114 study?

14 A. No.

15 Q. Did it disappoint you at the time that that

16 decision was made?

17 A. I don't remember.

18 Q. Do you know why it was considered not to be a

19 viable option at that time?

20 A. No.

21 Q. Do you have any further knowledge on that

22 decision?

23 A. No.

24 Q. Do you recall receiving word of the decision?

25 A. No, I don't remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Do you recall being generally aware that that
2 decision had been made in that time frame?

3 A. Yes, I guess.

4 MR. PHILLIPS: Well, don't guess, Dr.
5 McCarthy.

6 THE WITNESS: Yes.

7 BY MR. DAVIS:

8 Q. Did you generally appreciate back in that time
9 frame that not retaining a patient recruitment
10 firm for the 114 study meant that it was more
11 likely than not that you would not reach your
12 enrollment target?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: No.

15 BY MR. DAVIS:

16 Q. So even without the patient recruitment firm,
17 you believed that the 114 study would still
18 reach its enrollment target of 320 subjects?

19 MR. PHILLIPS: Objection.

20 THE WITNESS: I don't remember.

21 BY MR. DAVIS:

22 Q. Did you think that not hiring a patient
23 recruitment firm would negatively impact the
24 study's ability to reach its target enrollment?

25 A. No.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. So you didn't think it would matter one way or
2 the other?

3 A. I don't remember.

4 Q. Can you identify anyone else within Abbott who
5 participated in the decision to not retain the
6 patient recruitment firm?

7 A. Well, at least Marilyn Collicott, but beyond
8 that, I don't remember.

9 Q. What about Dr. Silber, did he participate in
10 that decision?

11 A. I don't remember.

12 Q. Is there anyone within Abbott other than Ms.
13 Collicott that you think may have played a role
14 in that decision?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: No, I don't.

17 (Marked for identification

18 Deposition Exhibit No. 22.)

19 BY MR. DAVIS:

20 Q. Dr. McCarthy, you have what has been marked as
21 Exhibit 22 of your deposition. I'd ask you to
22 look at this document and tell me if you've ever
23 seen it before.

24 A. Yes.

25 Q. When did you first see this document?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. I believe yesterday.

2 Q. Do you recall ever receiving a copy of this

3 document or any version of this document, a

4 descriptive memo, for ABT-594 while you worked

5 at Abbott?

6 A. I don't remember.

7 Q. Do you recall ever being asked by anyone at

8 Abbott to provide any information concerning

9 ABT-594 to be provided to John Hancock?

10 A. No.

11 Q. Do you recall ever receiving any requests from

12 anyone at Abbott to provide information

13 concerning 594 to be provided to any potential

14 investors in the development of 594?

15 A. No.

16 Q. Did you get a chance to read this document when

17 you looked at it yesterday?

18 A. No, not read the document.

19 Q. If you take a look at -- I think we went through

20 this yesterday -- it's page 8, like all pages of

21 this descriptive memorandum, but it's the page

22 that has the Bates number that ends in 4606.UR.

23 Do you have that page?

24 A. Yes.

25 Q. There is a section titled Product slash

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Development Background with a subsection titled

2 Clinical Studies. Do you see that?

3 A. Yes.

4 Q. To your knowledge, did you provide any of the

5 information that's contained here?

6 A. Not to my knowledge.

7 Q. It says:

8 Human clinical trials began

9 in 1997.

10 Is that true, to the best of your

11 knowledge?

12 A. Yes.

13 Q. It says:

14 Phase I trials with an oral

15 solution formulation indicated that

16 150 micrograms per day would be the

17 maximum tolerated dose. Results from

18 subsequent phase I and phase II

19 trials with soft elastic capsule and

20 hard gelatin capsule suggest that

21 higher doses would be tolerated.

22 Phase IIa studies with ABT-594 SEC

23 formulation suggested a trend towards

24 analgesic effect at 75 micrograms

25 BID.

1 What does BID stand for?

2 A. Twice a day.

3 Q. It says:

4 ABT-594 was generally well

5 tolerated in these studies.

6 Was ABT-594 generally well tolerated in

7 the prior phase I and phase II studies?

8 MR. PHILLIPS: Objection.

9 THE WITNESS: I'm not sure how to

10 answer that. I think -- can you ask the

11 question again? Sorry.

12 BY MR. DAVIS:

13 Q. Sure. Was ABT-594 generally well tolerated in

14 the prior phase I and phase II studies of

15 ABT-594?

16 A. I would say yes. Yes.

17 Q. Did you believe that the emesis problems that

18 had been encountered in some of those trials

19 were a sign of the compound being well

20 tolerated?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: No.

23 BY MR. DAVIS:

24 Q. Do you see any reference in this paragraph to

25 the emesis problems that you and others in

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Abbott had identified as far back as 1998?

2 A. The last sentence of the first paragraph

3 describes most common adverse events for

4 subjects receiving ABT-594 75 micrograms twice a

5 day includes vomiting, five percent.

6 Q. Did you understand that only five percent of the

7 people -- did you understand the results of the

8 clinical trials that were run on ABT-594 prior

9 to the 114 trial indicated that only five

10 percent of the people experienced vomiting?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: No.

13 BY MR. DAVIS:

14 Q. What was your understanding of approximately the

15 number of people who participated in those

16 trials who experienced vomiting?

17 MR. PHILLIPS: Objection.

18 THE WITNESS: I don't know.

19 BY MR. DAVIS:

20 Q. Was it greater than five percent?

21 A. I don't know.

22 Q. It wasn't less than five percent?

23 A. No, it was not less than five percent.

24 Q. And then says:

25 A phase IIb study for

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Do you have any recollection of reviewing
2 timelines for proposed patient recruitment
3 projects involving 594?

4 A. No.

5 Q. Who is Melissa Brotz, B-r-o-t-z?

6 A. Melissa Brotz? She was, I believe, in the
7 department of public affairs.

8 Q. What responsibilities did she have concerning
9 594?

10 A. I believe she was helping with -- helping
11 Marilyn develop patient recruitment strategies,
12 leveraging public affairs, advertising know-how.

13 Q. Was she involved in some way in the patient
14 recruitment project that was being considered
15 for 594?

16 A. Yes.

17 Q. What were her responsibilities in that respect?

18 A. By providing advertising and public affairs
19 know-how.

20 Q. Who was Jennifer Smoter?

21 A. I believe Jennifer worked for Melissa Brotz and
22 had the same functional role on the team.

23 (Marked for identification

24 Deposition Exhibit No. 25.)

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Dr. McCarthy, I would ask you to look at this
2 document and tell me whether you participated in
3 the creation of this document.

4 A. I would have participated in the creation of
5 certain slides for this document.

6 Q. This is a project review for ABT-594; correct?

7 A. It appears to be.

8 Q. And the date of the presentation is
9 November 17th, 2000. Does that mean that's the
10 date on which the presentation was made?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: I don't know.

13 BY MR. DAVIS:

14 Q. Is that typically the case?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: I don't -- I would be
17 speculating.

18 BY MR. DAVIS:

19 Q. Do you recall making a project -- or undertaking
20 a project review of 594 in November 2000?

21 A. No.

22 Q. Do you recall undertaking any sort of project
23 reviews with respect to 594?

24 A. Yes.

25 Q. Who would participate in the project reviews?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. Well, members of the team, including myself, the
2 operations manager, oftentimes the commercial
3 representative, regulatory representative,
4 toxicology representative, and the other
5 attendees would vary with the context of what
6 type of review it was.

7 Q. Do any members of Abbott's more senior
8 management attend the project reviews?

9 A. At times.

10 Q. So would there have been someone at this
11 particular project review, do you believe, above
12 Dr. Silber?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: I don't remember.

15 BY MR. DAVIS:

16 Q. Did someone from Abbott's more senior
17 management, someone above Dr. Silber, typically
18 attend the project reviews?

19 MR. PHILLIPS: Objection.

20 THE WITNESS: Yes.

21 BY MR. DAVIS:

22 Q. If you see in the very first page in Exhibit 25
23 there is an agenda with various topics and looks
24 like presenters. Do you see that?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. You are one of the presenters for clinical
2 results; correct?

3 A. Yes.

4 Q. Were these people presenting to someone other
5 than themselves or just within the group?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: I don't know.

8 BY MR. DAVIS:

9 Q. Typically the project reviews, were they
10 presenting to someone other than the group as a
11 whole or just to the group?

12 A. Typically, yes.

13 Q. Typically to someone other than the group as a
14 whole?

15 A. Yes.

16 Q. You just right now can't recall who?

17 A. Yes.

18 Q. What were the purposes of the project reviews?

19 A. There were different purposes.

20 Q. Do you recall the purpose of this project
21 review?

22 A. No.

23 Q. If you'd look at the page, please, that's Bates
24 numbered 9108, there is a slide in the lower
25 right-hand corner titled ABT-594 Overview. Do

1 you see that?

2 A. Yes.

3 Q. And it refers at the bottom to:

4 Phase IIb in painful

5 diabetic neuropathy, using titrated

6 doses up to 300 micrograms BID is

7 ongoing.

8 Do you see that?

9 A. Yes.

10 Q. That's a reference to the 114 study?

11 A. Yes.

12 Q. If you turn to the very next page, the next

13 slide says:

14 ABT-594 issues. Dropout

15 rate in current phase IIb study is

16 about 30 percent.

17 Do you see that?

18 A. Yes.

19 Q. Did you create these two slides?

20 A. I don't know.

21 Q. Why was it an issue as of October -- I'm sorry,

22 as of November 2000 that the dropout rate in the

23 phase IIb study was about 30 percent?

24 A. I don't know.

25 Q. You have no recollection of that?

1 A. No.

2 Q. Was that a cause for concern at that point in

3 time within Abbott?

4 MR. PHILLIPS: Objection.

5 THE WITNESS: I don't remember.

6 BY MR. DAVIS:

7 Q. If you'd look, please, in the pages that -- the

8 page that ends 9124. Do you see that there are

9 slides there that begin Milestone Criteria?

10 A. Yes.

11 Q. You were one of the presenters for this section

12 of the review?

13 A. I don't remember.

14 MR. PHILLIPS: Objection.

15 BY MR. DAVIS:

16 Q. It lists your name there. Does that lead you to

17 believe that you are one of the presenters?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: I don't remember.

20 BY MR. DAVIS:

21 Q. Just to the right of that slide there is a slide

22 that says:

23 M99-114 sample size

24 rationale.

25 Do you see that?

1 A. Yes.

2 Q. And there is a reference there to N equals 320.

3 Is that the number of anticipated or target

4 subjects in the trial?

5 MR. PHILLIPS: Objection.

6 THE WITNESS: I don't know.

7 BY MR. DAVIS:

8 Q. There is a reference to type 1 error 0.05. What

9 does that refer to?

10 MR. PHILLIPS: Objection.

11 THE WITNESS: Type 1 error would have

12 been a variable that the statisticians use to

13 characterize the study.

14 BY MR. DAVIS:

15 Q. What does it mean?

16 MR. PHILLIPS: Objection.

17 THE WITNESS: I would not be able to

18 give a good description of type 1 error.

19 BY MR. DAVIS:

20 Q. Just below the reference to type 1 error, there

21 is reference to power 80 percent. Do you see

22 that?

23 A. Yes.

24 Q. What does that mean?

25 MR. PHILLIPS: Objection.

1 THE WITNESS: Similarly, a descriptive
2 term for the study, that the statisticians use
3 to describe the study.

4 BY MR. DAVIS:

5 Q. What is your understanding as to the
6 significance or meaning of power in the context
7 of one of these clinical trials?

8 A. An estimate that the study would be able to
9 detect a certain magnitude treatment effect.

10 Q. And what does the 80 percent represent? Is that
11 a confidence level?

12 MR. PHILLIPS: Objection.

13 THE WITNESS: Yes.

14 BY MR. DAVIS:

15 Q. So is it fair to say that this 114 study was
16 designed such that they would have an 80 percent
17 confidence level based upon the data that the
18 effect of the compound, if any, observed in the
19 trial was the result of the compound and not
20 some other factor?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: No.

23 BY MR. DAVIS:

24 Q. What would the 80 percent confidence level be
25 in?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 MR. PHILLIPS: Same objection.

2 THE WITNESS: In a prespecified

3 magnitude of a treatment effect, not the

4 observed treatment effect.

5 BY MR. DAVIS:

6 Q. There is a reference there to effect size as

7 well. Do you see that?

8 A. Yes.

9 Q. What does that mean?

10 MR. PHILLIPS: Objection.

11 THE WITNESS: I don't know in this

12 context. In general it would be assumed to be

13 the prespecified effect size.

14 BY MR. DAVIS:

15 Q. Would having a -- to your knowledge, would

16 having less than 320 subjects in the study

17 affect the power of the study?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: Yes.

20 BY MR. DAVIS:

21 Q. Would it affect it adversely?

22 MR. PHILLIPS: Objection.

23 THE WITNESS: I would be speculating as

24 to whether it's adverse.

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Would you expect that having less than 320
2 subjects would enhance the power of the study?

3 MR. PHILLIPS: Objection.

4 THE WITNESS: No.

5 BY MR. DAVIS:

6 Q. So if it affected it, more likely than not, it
7 would be an adverse affect; is that right?

8 MR. PHILLIPS: Objection.

9 THE WITNESS: I would still be
10 speculating. It would be a pure judgment in
11 what ways it was adverse.

12 BY MR. DAVIS:

13 Q. Who is David Morris?

14 A. He was the statistician.

15 Q. Did you know Jim Thomas as well?

16 A. Yes.

17 Q. Was he also a statistician?

18 A. Yes.

19 Q. Does Mr. Morris still work for Abbott?

20 A. I don't know.

21 Q. Have you kept in touch with anyone at Abbott who
22 worked on the 594 project with you?

23 A. No.

24 Q. When was the last time you had any
25 communications with anyone at Abbott regarding

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 yesterday?

2 A. The top page, I remember the writing, but other

3 than that, it doesn't look familiar.

4 Q. Did you have periodic project team meetings when

5 you were working on the 594 project?

6 A. Yes.

7 Q. Did all the members of the team -- were all the

8 members of the team typically invited to these

9 project team meetings?

10 A. Yes.

11 Q. Where were they held?

12 A. At Abbott Park.

13 Q. Just in a conference room?

14 A. Yes.

15 Q. Approximately how many members on that project

16 team?

17 A. I don't remember.

18 Q. Again, you were not the head of the project

19 team, it was Dr. Silber; is that right?

20 A. It depends on when.

21 Q. At some point in time did you become head of the

22 594 project team?

23 A. Yes.

24 Q. When was that?

25 A. I don't remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. If you turn to the third page of this document,
2 Exhibit 26, under Key Activities, next three
3 months, then very near the bottom it says:
4 M99-114 enrollment cutoff.

5 What is an enrollment cut off?

6 A. I don't know.

7 Q. Was there an enrollment cutoff for the 114
8 trial?

9 A. I don't remember.

10 (Marked for identification
11 Deposition Exhibit No. 27.)

12 BY MR. DAVIS:

13 Q. Dr. McCarthy, you have Exhibit 27 in front of
14 you. Have you seen this document before?

15 A. I don't remember. I may have seen it yesterday,
16 but I'm not sure.

17 Q. On its face it appears to be another project
18 status report for ABT-594, this one dating from
19 December 2000. And under the various areas
20 here -- let me just ask you, the venture area,
21 that was your area; correct?

22 A. Yes.

23 Q. But there is also a PARD. What is that?

24 A. I don't remember what the acronym stands for,
25 but it was the formulation and manufacturing

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Certainly. Do you recall a decision being made
2 within Abbott sometime in late 2000 to end the
3 enrollment in the 114 trial at a date that had
4 been planned -- a date earlier than had been
5 planned to that point?

6 A. No, I don't remember.

7 Q. I'll represent to you that there are documents
8 in this case and testimony from Ms. Collicott
9 yesterday that a decision was made in late 2000,
10 at least conveyed to her, to move the end of
11 enrollment up from sometime in March or April of
12 2001 to January 5 of 2001. You have no
13 recollection of that?

14 A. I don't remember.

15 Q. Then I take it you don't recall who made that
16 decision?

17 A. No.

18 Q. You don't recall why the decision was made?

19 A. No.

20 (Marked for identification
21 Deposition Exhibit No. 28.)

22 BY MR. DAVIS:

23 Q. Dr. McCarthy, would you look at this document
24 for a moment, Exhibit 28, particularly the
25 section having to do with ABT-594, and tell me

1 when you are done reading that section, please.

2 A. I'm sorry, which section?

3 Q. A section about a third of the way down this

4 page that references ABT-594. Would you read

5 all the entries concerning ABT-594, and tell me,

6 please, when you are done.

7 A. I've done it.

8 Q. Does that refresh your recollection in any way

9 about a decision to close enrollment in the 114

10 trial approximately two months ahead of the

11 trial's most recent closing -- estimated closing

12 date of March 5?

13 A. No, not in this time frame.

14 Q. Do you have a recollection of some other

15 decision being made to speed up the enrollment

16 close date?

17 A. Other decision --

18 Q. Well, what do you recall having to do with the

19 enrollment dates of 114?

20 A. I remember that at some point late in the

21 conduct of the trial, we had discussions about

22 when to conclude the trial, and a decision was

23 made to stop the study with fewer patients than

24 originally planned. But I don't remember when

25 exactly those decisions were made or discussed.

1 Q. When you say we, do you recall having

2 discussions on that topic?

3 A. Yes.

4 Q. Who did you have discussions with?

5 A. At the very least, with -- within the team,

6 Marilyn and I, and I don't recall who we had

7 discussions with, whether it was Chris Silber or

8 Marleen Verlinden.

9 Q. Who made the decision to end the study early?

10 A. I don't remember.

11 Q. Was it explained to you at the time why the

12 decision was made to end the study early?

13 A. I have the sense that it was, but I don't

14 remember the context.

15 Q. Do you have any recollection of the reasoning

16 that was conveyed to you behind the decision to

17 end the study early?

18 A. Yes, I think I do.

19 Q. What do you recall?

20 A. That, on balance, the benefits of getting to the

21 conclusion of the study sooner outweighed any

22 increased costs of continuing the study; that

23 because of the delays in enrollment, to complete

24 the study would have taken longer amounts of

25 time and greater amounts of investment with, you

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

- 1 know, marginal improvements in understanding --
- 2 understanding the performance of the drug.
- 3 Q. Did the decision to end enrollment early have
- 4 anything to do with the adverse events that were
- 5 being suffered in the course of the trial?
- 6 A. No.
- 7 Q. Did it have anything to do with the premature
- 8 termination rate that was being experienced?
- 9 A. Not directly.
- 10 Q. Did it have any relationship to that at all,
- 11 either directly or indirectly?
- 12 A. Indirectly.
- 13 Q. How so?
- 14 A. As I mentioned before, investigators may have
- 15 been less likely to enroll the next patient
- 16 based on the experiences they encountered with
- 17 prior patients, and so that might have
- 18 contributed to slowing enrollment.
- 19 Q. Now, was the decision to end the study early
- 20 made by Dr. Silber or someone above Dr. Silber?
- 21 MR. PHILLIPS: Objection.
- 22 THE WITNESS: I don't remember.
- 23 BY MR. DAVIS:
- 24 Q. You didn't make the decision?
- 25 A. No, I wouldn't have made the decision.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Did you have the authority to make that
2 decision?

3 A. No.

4 Q. So it would have had to have been somebody above
5 you?

6 A. Yes.

7 Q. Was Dr. Silber aware of the decision to end the
8 study early?

9 A. I don't remember.

10 Q. Do you expect that that's something that was
11 important enough that you would have conveyed it
12 to Dr. Silber, if he wasn't already aware of it?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: No. The only way I can
15 describe it is what I don't remember is actually
16 who I was reporting to at that time. There was
17 a change, and I worked variously for Chris
18 Silber and for a period of time reported to John
19 Leonard and then to Marleen Verlinden, and I
20 honestly don't remember who were the people that
21 I had an obligation to, you know, advise,
22 recommend, and then have them make a decision
23 and respond to.

24 BY MR. DAVIS:

25 Q. Let me go back and broaden the questions a

1 A. Yes.

2 Q. So it was a decision made somewhere above you;

3 correct?

4 A. At the time that it was made.

5 Q. Did you at some point in time convey to your

6 superiors that the study had, in fact, been

7 terminated early?

8 MR. PHILLIPS: Objection.

9 THE WITNESS: Say that one again.

10 BY MR. DAVIS:

11 Q. Did you at some point in time convey to your

12 superiors that the study had, in fact, been

13 terminated early?

14 A. I don't know.

15 Q. It says here also that:

16 This is two months ahead of

17 our most recent estimate of March 5

18 and will include less than our

19 original target of 320 patients.

20 Were you aware at the time that the

21 decision was made to end enrollment in the 114

22 study early, that it would result in less than

23 320 patients being enrolled?

24 A. Yes.

25 Q. Did you understand that that could affect the

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 statistical validity of the trial in some way?

2 MR. PHILLIPS: Objection.

3 THE WITNESS: No.

4 BY MR. DAVIS:

5 Q. You didn't think that it could affect the

6 statistical validity of the trial?

7 A. Correct.

8 Q. You didn't think it would have any impact at

9 all?

10 A. Yes.

11 Q. Even having less than 320 patients in the study

12 you thought would not impact the statistical

13 validity?

14 A. Yes.

15 Q. Why is that the case?

16 A. For the purposes of the study, the validity of

17 the study would be intact. The chances of

18 observing a prespecified treatment effect would

19 diminish, but -- right.

20 Q. Is it fair to say that you understood that

21 terminating the study early didn't mean that you

22 would not be able to get any useful information

23 from the study?

24 A. Correct.

25 Q. You were still expecting to get some useful

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 information from the study?

2 A. Yes.

3 Q. Yet you understood that statistically, the proof
4 of some of the information that you might obtain
5 from the study might be affected; is that
6 correct?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: I don't think I can
9 answer that.

10 BY MR. DAVIS:

11 Q. Just because you don't know?

12 A. Yeah.

13 Q. Do you recall any discussions while the 114
14 study was underway, discussions or
15 communications within Abbott to the effect that
16 the study was not going well?

17 A. Sorry, ask that again.

18 Q. Sure. Do you recall any discussions or
19 communications within Abbott while the 114 study
20 was underway to the effect that the study was
21 not going well or did not appear to be going
22 well?

23 MR. PHILLIPS: Objection.

24 THE WITNESS: Yes.

25 BY MR. DAVIS:

1 Q. What do you recall in that regard?

2 A. The discussions about slow enrollment.

3 Q. Anything else?

4 A. No.

5 Q. Do you recall any discussions with anyone or
6 communications with anyone within Abbott while
7 the 114 study was underway concerning the
8 possibility that the results of the study would
9 indicate that 594 was not being well tolerated
10 by the subjects of the study?

11 MR. PHILLIPS: Objection.

12 THE WITNESS: Can you ask that again?

13 Sorry.

14 BY MR. DAVIS:

15 Q. Let me rephrase it. As the 114 study
16 progressed, you were aware that there were a
17 significant number of adverse events involving
18 nausea and vomiting in the course of the study;
19 correct?

20 MR. PHILLIPS: Objection.

21 THE WITNESS: I don't know that there
22 was a significant number.

23 BY MR. DAVIS:

24 Q. Do you know what the final termination rate,
25 premature termination rate was in the study?

1 A. No.

2 Q. Do you recall it was close to 50 percent?

3 A. I don't remember.

4 Q. If it was close to that, would you regard that

5 as a significant premature termination rate?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: I wouldn't -- no.

8 BY MR. DAVIS:

9 Q. How many -- is a 50 percent or, say, 47 to 50

10 percent premature termination rate among

11 clinical trials that you've been involved in

12 normal?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: There is a distribution

15 of discontinuation rate, so it's hard for me to

16 answer what a normal -- there is a distribution.

17 So I don't think that's the average.

18 BY MR. DAVIS:

19 Q. Did the discontinuation rate in the 114 study

20 concern you?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: No.

23 BY MR. DAVIS:

24 Q. Not at all?

25 A. No.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Did you ever hear anyone within Abbott express
2 any concern about the discontinuation rate, the
3 premature discontinuation rate on the study?

4 A. Yes.

5 Q. What do you recall in that regard?

6 A. I think, in particular, I remember commercial
7 colleagues being concerned about that rate and
8 attempting to draw inferences of what it would
9 mean for the compound.

10 Q. Particularly who do you recall making comments
11 in that regard?

12 A. I don't remember particular people.

13 Q. When you say it was commercial colleagues, you
14 mean people working the commercial side of the
15 business?

16 A. Yes.

17 Q. Were they team members?

18 A. Yes.

19 Q. I'm going to, if we can, just go back and find
20 that list of team members.

21 MR. DAVIS: Go off the record for a
22 minute.

23 (Discussion held off the record.)

24 BY MR. DAVIS:

25 Q. Dr. McCarthy, would you look at Exhibit 26 for a

1 moment, please, second page of Exhibit 26.

2 A. Yes.

3 Q. There is a list of agenda area updates for a 594

4 project team meeting. Do you see that?

5 A. Yes.

6 Q. There are a couple of people listed here for

7 commercial?

8 A. Yes.

9 Q. Landsberg, Robinson. Who was Mr. or Ms.

10 Landsberg?

11 A. Andrea Landsberg and Laura Robinson.

12 Q. Are either Ms. Landsberg or Ms. Robinson the

13 commercial people that you referred to a few

14 moments ago expressing concerns about the

15 implications of the adverse events that were

16 being experienced or the premature terminations

17 that were being experienced in the 114 study?

18 A. I can't remember if it was particularly Andrea

19 or Laura. We had at least a few different

20 commercial people come through the team. So I

21 have, more than anything, a general sense of

22 whichever commercial person it happened to be at

23 the time.

24 Q. What else do you recall about those discussions,

25 the discussions within Abbott about the

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 potential implications of the premature
2 terminations or the adverse events that were
3 being experienced in the 114 trial?

4 A. I think it was -- those conversations were
5 fairly -- were consistent and limited. The
6 commercial folks who generally -- well, had no
7 experience in clinical trials would try to infer
8 something about the future potential of the
9 drug, the product profile, so that they could
10 update their views on emerging information;
11 whereas on the R&D side of the equation, of
12 people who were very familiar with trials, we
13 were -- you know, had the experience to know
14 that it was not informative to try and draw
15 conclusions from that, that across different
16 clinical trials dropout rates can vary
17 dramatically, and that the only informative time
18 to understand the implications of the results
19 were at the conclusion of the study.

20 Q. So you didn't draw any preliminary or tentative
21 conclusions from any of the adverse event data
22 or the premature termination data before the
23 study was unblinded?

24 A. I did not.

25 Q. You didn't have a sense one way or the other how

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 it was going?

2 A. No.

3 (Marked for identification

4 Deposition Exhibit No. 29.)

5 BY MR. DAVIS:

6 Q. Dr. McCarthy, please look at this document.

7 It's Exhibit 29. Tell me if you've seen it

8 before.

9 A. I believe I saw it yesterday.

10 Q. When did you see it last before yesterday?

11 A. I don't recall seeing it before yesterday.

12 Q. Do you recall that a letter went out in around

13 December of 2000 notifying the site

14 investigators that -- or the investigation

15 sites, I'm sorry, that the study was being

16 terminated early?

17 A. I don't remember that letters were sent in

18 December of 2000.

19 Q. The cover e-mail says it's from Marilyn

20 Collicott. She was in charge of administering

21 the trial; is that right?

22 A. Yes.

23 Q. It's an e-mail to John Schanzenbach. Do you

24 know who John Schanzenbach was?

25 A. I don't know. The name is familiar, but I don't

1 know.

2 Q. The e-mail references:

3 The attached letter which

4 explains our reasoning.

5 Do you see that?

6 A. Yes, I see that.

7 Q. And if you take a look at the letter, the second

8 paragraph of the letter begins:

9 As specified in the

10 protocol.

11 Would you just read that paragraph to

12 yourself and tell me when you are done, please.

13 A. I finished reading the paragraph.

14 Q. Does that paragraph accurately describe the

15 reasoning behind the decision to terminate the

16 114 study early?

17 A. Yes.

18 Q. And did you appreciate at the time the decision

19 was made to terminate the study early, that you

20 would not reach the preplanned 80 percent

21 statistical power as a result?

22 A. I don't remember.

23 Q. Do you recall anything else other than what

24 you've testified to concerning the decision to

25 end the 114 study early?

1 A. No.

2 (Marked for identification

3 Deposition Exhibit No. 30.)

4 BY MR. DAVIS:

5 Q. Dr. McCarthy, I'll show you what's been marked

6 as Exhibit 30 at your deposition and ask you if

7 you've seen this document before.

8 A. I may have seen it yesterday.

9 Q. When is the last time you saw it before that?

10 A. I don't recall seeing it.

11 Q. This on its face appears to be another project

12 status report for ABT-594, this one dated from

13 January of 2001.

14 The first bullet point under monthly

15 highlights states:

16 Enrollment closed for our

17 phase IIb painful diabetic

18 polyneuropathy trial, M99-114, with

19 total enrollment reaching 269.

20 Is that consistent with your

21 recollection?

22 A. Yes.

23 Q. It says:

24 The last patient will

25 complete the study at the end of

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 February and results will be
2 available at the end of May.

3 What results were expected to be
4 available at the end of May?

5 A. I don't recall.

6 Q. Under progress gauges it indicates:

7 Prepare study closeout
8 timelines.

9 Is that something that you worked on?

10 A. No, Marilyn Collicott would have defined --
11 would have put together the study closeout
12 timelines.

13 Q. Did you have any responsibility with respect to
14 helping to collect data, review data, clean up
15 data with respect to this trial?

16 A. Yes.

17 Q. What responsibilities did you have?

18 A. I would have reviewed -- I would have reviewed
19 inquiries generated by data management on the
20 data that was brought in-house, and in
21 particular, reviewed safety data to ensure its
22 completeness and accuracy.

23 Q. The data that is collected from the trial is
24 reviewed and cleaned up, so to speak, in order
25 to ensure that it's reasonably complete; is that

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 right?

2 MR. PHILLIPS: Objection.

3 THE WITNESS: It's reviewed and cleaned

4 up to ensure that it's, you know, as accurate as

5 it possibly could be, yes.

6 BY MR. DAVIS:

7 Q. Once that process is done, is the data then

8 locked?

9 A. Yes.

10 Q. You've heard that term?

11 A. Yes.

12 Q. What does that mean?

13 A. From -- it's effectively a version control

14 mechanism. So when all of the inquiries that

15 have been generated through the cleanup process

16 have all been resolved and all the data have

17 been adjusted, then the database is locked, it's

18 defined as a fixed data set, and then and only

19 then can the database be unblinded.

20 Q. When was the data for this study locked?

21 A. I don't remember.

22 Q. Who was responsible for locking it?

23 A. I believe Abbott SOP's had the statistician

24 responsible for designating the database lock.

25 Q. Who was that on this project, the 594 project?

1 Q. On the paragraph for 594, the first paragraph
2 under progress, the last line of that paragraph
3 states:

4 This acceleration of the
5 study close date was driven by our
6 desire to evaluate the outcome of the
7 study, and an assessment of the
8 statistical power of the study.

9 What do you recall -- what discussions
10 or communications do you recall within Abbott on
11 that topic?

12 A. Well, I don't know what this is referencing, but
13 as I mentioned before, we were interested in
14 understanding the outcome of the study, and as I
15 described before, we worked with the
16 statisticians to come to the conclusion that
17 continuing to try and enroll patients was not
18 going to meaningfully change our ability to make
19 decisions from the trial.

20 Q. Did you have any understanding at that point in
21 time as to what likely decisions would be made
22 as a result of the outcome of the trial?

23 A. Yes.

24 Q. What?

25 A. The decision to continue or discontinue

1 development.

2 Q. And did you have any understanding or belief as

3 to which of those decisions was more likely than

4 the other?

5 A. No, I didn't.

6 Q. Looking back again at Exhibit 30, under February

7 projections, there is a reference to a project

8 review with Jeff Leiden and senior management.

9 Did you participate in that review?

10 A. I don't know.

11 Q. Do you recall participating in a review of the

12 594 project shortly after the study ended?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: I don't recall a project

15 review shortly after the study ended.

16 BY MR. DAVIS:

17 Q. Do you recall a project review shortly after the

18 enrollment was terminated?

19 A. No.

20 Q. Do you have any recollection of any project

21 reviews with Dr. Leiden?

22 A. Yes.

23 (Marked for identification

24 Deposition Exhibit No. 31.)

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Do you recall giving any information to Mr.
2 Biarnesen or anyone else at Abbott in the late
3 2000 time frame in which you were trying to come
4 up with probabilities for ABT-594, based in part
5 on preliminary data from the 114 trial?

6 A. No.

7 Q. Do you recall being asked in that time frame to
8 come up with probabilities or projections
9 regarding the likely success of the compound
10 over time?

11 A. Not in that specific time frame, but there was a
12 continuing conversation on every project about
13 probabilities of technical success.

14 Q. Is this part of that continuing conversation?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: I don't know if this was
17 or not.

18 BY MR. DAVIS:

19 Q. Well, there are references here to Chris and
20 Bruce and Mike on this page. Are you aware of
21 any other Bruces working on the neuropathic pain
22 ABT-594 trial?

23 A. No.

24 Q. Is it your testimony that you didn't participate
25 in any probability exercises in that time?

1 A. No.

2 Q. If you had participated in any probability

3 exercises at that point in time, would you have

4 taken into account the preliminary information

5 that you had from the 114 trial?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: No.

8 (Marked for identification

9 Deposition Exhibit No. 32.)

10 BY MR. DAVIS:

11 Q. Dr. McCarthy, would you read this document to

12 yourself, and then tell me when you are done.

13 A. I'm done.

14 Q. Have you seen this document before?

15 A. Yes.

16 Q. Did you see it yesterday?

17 A. Yes.

18 Q. Now, who's Elizabeth Kowaluk?

19 A. She was also in that decision analysis group and

20 I believe worked for Steve Kuemmerle.

21 Q. Did you work with Elizabeth Kowaluk with respect

22 to ABT-594?

23 A. Yes.

24 Q. And what did Ms. Kowaluk do?

25 A. She was the decision analysis -- I guess point

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 cast. At SAC today, Jeff Leiden put
2 up a slide today listing ABT-822 as
3 commercial viability questionable.
4 Of course, ABT-594 was painted with
5 the same brush. Bryan.

6 Did I read that correctly?

7 A. Yes.

8 Q. Now, what is SAC?

9 A. I don't remember.

10 Q. Were you aware in the November or late 2000 time
11 frame that Jeff Leiden had identified ABT-594 as
12 having questionable commercial viability?

13 MR. PHILLIPS: Objection.

14 THE WITNESS: No.

15 BY MR. DAVIS:

16 Q. Is that something that Ms. Kowaluk shared with
17 you?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: No.

20 BY MR. DAVIS:

21 Q. Were you present at any meetings at which Dr.
22 Leiden identified ABT-594 as having questionable
23 commercial viability?

24 A. Not that I remember.

25 Q. Had you provided any information to Dr. Leiden

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 probability of success of 32 percent at that

2 point in time?

3 A. Okay, I see that.

4 Q. Did you contribute -- to your knowledge, did you

5 contribute in any way to the calculation of that

6 number?

7 A. I don't know.

8 Q. Do you know whether -- do you know who prepared

9 this document?

10 A. No.

11 (Marked for identification

12 Deposition Exhibit No. 37.)

13 BY MR. DAVIS:

14 Q. Dr. McCarthy, you have Exhibit 37 in front of

15 you. I'll ask you if you have seen that

16 document before.

17 A. No.

18 Q. Did you -- have you seen versions of this

19 document before?

20 A. Multiple slides in this document are familiar.

21 Q. If you'd take a look at the page that Bates

22 number ends in 2359 for a moment. It appears to

23 be a title page for a slide presentation on

24 ABT-594; is that right?

25 A. It appears to be.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Do you believe that you were at this

2 presentation?

3 A. I don't remember.

4 Q. I'll represent to you that we have lots of

5 documents that point to a presentation to Dr.

6 Leiden on February 2nd, 2001, and again, we just

7 saw a document in which I think Ms. Kowaluk was

8 asking you whether you needed anything further

9 for that presentation.

10 Did that refresh your recollection on

11 whether you were a participant in a presentation

12 to Dr. Leiden in or around February 2nd of 2001?

13 A. It's the date part that I just don't remember.

14 Q. Do you have any reason to believe that the

15 presentation to Dr. Leiden that you do recall

16 did not occur on February 2nd, 2001?

17 A. Yeah, I don't remember when it occurred.

18 Q. What do you recall from that presentation?

19 A. Actually, I don't remember much about -- well, I

20 just don't remember a presentation at that time,

21 to be honest.

22 Q. Did Dr. Silber participate in the presentation

23 with you?

24 A. I don't remember.

25 Q. Take a look at the next page. It shows an

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 agenda for presentation, and it lists you as

2 addressing clinical overview and go/no go

3 process. Are those topics that you recall

4 addressing in a presentation to Dr. Leiden?

5 A. Yes, actually.

6 Q. Now, if you turn, please, to the page Bates

7 numbered 2389, the last four digits of the Bates

8 number. Are these -- beginning here, are these

9 slides that you prepared or participated in

10 preparing?

11 MR. PHILLIPS: Beginning here, but

12 ending where?

13 BY MR. DAVIS:

14 Q. Well, actually, why don't you take a look,

15 please, and first tell me whether you prepared

16 any of these slides or participated in the

17 preparation of any of these slides?

18 A. I participated in the preparation starting on

19 slide 2390 and --

20 Q. Going to where?

21 A. I believe all of the slides from 2390 to 2434

22 were slides that I participated in the creation

23 of.

24 Q. 2434 you said?

25 A. 2434. Slide ABT-594 take home messages is the

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 last one for that block.

2 Q. Would you look at the page that's Bates numbered

3 2391. Do you have that page in front of you?

4 A. Yes.

5 Q. It says here:

6 ABT-594 definitely not a

7 take home message for today.

8 Now, what was definitely not the take

9 home message that you were identifying here?

10 A. The message that was to be conveyed by the slide

11 was that we were not at this point -- and again,

12 I don't remember when -- I don't actually

13 remember when this presentation was, but that

14 the message was not that we knew what 594 would

15 definitively do, whether it would or would not

16 satisfy -- or will or will not satisfy the unmet

17 need because, if I remember correctly the

18 context of this presentation, we did not have

19 the results from the study that would help us to

20 conclude that.

21 So it was at the very beginning of my

22 presentation effort to clearly articulate or set

23 expectations what management should not try and

24 do at that setting.

25 Q. Is it fair to say that you wanted to emphasize

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 the point that management should not come to the
2 conclusion that 594 would necessarily be a
3 commercially viable drug at that point in time?

4 MR. PHILLIPS: Objection.

5 THE WITNESS: That they should not
6 conclude that we had the information yet to make
7 the decision.

8 BY MR. DAVIS:

9 Q. If you would look, please, at page Bates
10 numbered 2430.

11 A. 2430, yes.

12 Q. That's reference to the -- it says phase IIb,
13 and one of the phase IIb trials mentioned there
14 was the 114 trial; correct?

15 A. Yes.

16 Q. And if you look to the next page, there is a
17 slide that's specific to the 114 trial; correct?

18 A. Yes.

19 Q. Did you, in the course of your presentation,
20 explain to Dr. Leiden and others the design of
21 the 114 trial?

22 MR. PHILLIPS: Objection.

23 THE WITNESS: I don't remember who --
24 whether Jeff was there or others were there, but
25 I do, you know, remember a presentation that,

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 you know, we had updated people, management --
2 again, I can't remember who was there -- on our
3 information to date.

4 BY MR. DAVIS:

5 Q. And if you would turn two more pages into this
6 document to the page that's Bates numbered 2433,
7 there is a slide there having to do with M99-114
8 status. Do you see that?

9 A. Yes.

10 Q. One of the things you noted was that the
11 enrollment has ended on 1-5-01 at 269 subjects;
12 is that correct?

13 A. Yes.

14 Q. Did you think it was important at the time that
15 you let Abbott's management know that that trial
16 had ended on 1-5-01 at less than the target
17 number of subjects?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: No.

20 BY MR. DAVIS:

21 Q. So you put this in here just because you thought
22 it might be interesting?

23 MR. PHILLIPS: Objection.

24 THE WITNESS: I put it in there to
25 identify that the study had ended.

1 BY MR. DAVIS:

2 Q. Were you trying to convey information that you

3 thought was important to Abbott's management?

4 MR. PHILLIPS: Objection. You are

5 arguing with the witness, Counsel.

6 MR. DAVIS: No, I think that's a

7 legitimate question.

8 THE WITNESS: I think I would say that

9 informing Abbott's management of the conclusion

10 of an enrollment is inherently important.

11 BY MR. DAVIS:

12 Q. It is or is not?

13 A. Is.

14 Q. Then you also noted that the prespecified power

15 was not reached?

16 A. Yes.

17 Q. Did you regard that as important to let them

18 know?

19 A. Yes.

20 Q. Why did you think it was important to let them

21 know that?

22 A. Because it's two parts of the -- two parts of

23 the rationale for -- it's one of two parts for

24 the rationale of stopping the study early, going

25 back to the idea that the benefits -- there were

1 marginal benefits to continuing the study; so
2 that despite not reaching the prespecified
3 power, the statistical components of the study
4 weren't going to be affected because our
5 discussions with statistics strongly suggested
6 that we would be able to make informed decisions
7 about how to proceed with the information that
8 we would have with fewer subjects enrolled.

9 Q. And when you showed this slide in the course of
10 your presentation, did you discuss the premature
11 terminations that had been experienced in the
12 trial?

13 A. Not that I recall.

14 Q. Did you discuss with Abbott's management the
15 adverse events that had been experienced?

16 MR. PHILLIPS: Objection.

17 THE WITNESS: Well, no. No.

18 BY MR. DAVIS:

19 Q. Did you explain why it was that you ended
20 enrollment early?

21 A. Yes.

22 Q. What did you tell them?

23 A. That enrollment had been slow, that the benefits
24 of continuing to try and enroll the remaining
25 patients were marginal given the information

1 that we believed we could continue to get out of
2 the study to make informed decisions, as opposed
3 to the time and cost to get to some
4 non-meaningful additional number of patients.

5 Q. Further down the same slide, there is reference
6 to database release 5-01. Is that a reference
7 to May of '01?

8 A. That's what I would infer from the slide.

9 Q. And what is database release?

10 A. In Abbott terminology, that would have been the
11 coincidental or just before database lock or
12 synonymous with database lock.

13 Q. And then you would expect unblinding would occur
14 after that; is that right?

15 A. Yes.

16 Q. Have you ever participated in any trial, either
17 at Abbott or any other location, where the trial
18 results were unblinded before the database was
19 locked?

20 A. No. I'm sorry, yes.

21 Q. When?

22 A. In unblinded studies.

23 Q. Have you ever participated in any double-blinded
24 studies in which the results of the trial were
25 unblinded before the database was locked?

1 A. I've participated in double-blind trials in
2 which individual patient results were unblinded
3 for safety reasons.

4 Q. Have you ever participated in any clinical
5 trials in which all of the -- strike that.

6 Have you ever participated in any
7 double-blinded clinical trials in which all of
8 the data was unblinded before it had been
9 locked?

10 A. No.

11 Q. Do you recall anything else other than what
12 you've testified to already concerning the
13 review, project review, that you made a
14 presentation at to Dr. Leiden and others at
15 Abbott?

16 A. No.

17 Q. Do you recall any discussion about the long-term
18 prospects for 594?

19 A. No.

20 Q. Was there any discussion about prospects for 594
21 generally?

22 A. No.

23 Q. Any discussion about any -- did you get any
24 feedback from any of the audience participants
25 regarding 594?

1 A. That I don't remember.

2 Q. Did you get any indication from them at all as
3 to what they were thinking in response to your
4 presentation?

5 A. Not that I remember.

6 Q. Either then or thereafter?

7 A. No, again, not that I remember.

8 Q. They were pretty much silent during the
9 presentation?

10 A. You know, I can't remember if people spoke or
11 asked questions or not, but I have the -- my
12 recollection of the discussion in which the
13 particular slides we went over and I described
14 were those that I made, my recollection was the
15 sense of leaving that meeting having, in a
16 sense, successfully updated folks on the status
17 of the project and kept people focused on
18 waiting for the results of the study in order to
19 be able to make a decision about the future of
20 the compound.

21 (Marked for identification
22 Deposition Exhibit No. 38.)

23 BY MR. DAVIS:

24 Q. Dr. McCarthy, I show you what has been marked as
25 Exhibit 38 at your deposition and ask you if

1 you've seen this document before.

2 A. No.

3 Q. Did you see this document yesterday?

4 MR. PHILLIPS: Objection. It's

5 attorney work product. Instruct the witness not

6 to answer.

7 MR. DAVIS: I think I can fairly ask

8 him whether he saw this document yesterday.

9 MR. PHILLIPS: I don't think you can.

10 I think you can ask him if he's seen the

11 document before, but I don't think you can ask

12 him if he's seen the document yesterday.

13 MR. DAVIS: You're instructing him not

14 to answer that question?

15 MR. PHILLIPS: I am.

16 BY MR. DAVIS:

17 Q. You don't recall seeing this document before?

18 A. I don't.

19 Q. It appears to be e-mail between you and Ms.

20 Kowaluk. If you'd look at the bottom of the

21 first page, it appears to be an e-mail from you

22 to Ms. Kowaluk dated February 2nd, 2001. Do you

23 see that?

24 A. Yes.

25 Q. The subject is DSG. Do you see that?

1 A. Yes.

2 Q. And the next page is a continuation of the same

3 e-mail. It states:

4 When we discuss scope and

5 frame during our first meeting, we

6 will want to discuss several issues

7 that came up at today's Leiden

8 meeting, though I think these are not

9 necessarily new.

10 Do you see that?

11 A. Yes.

12 Q. This is you writing to Ms. Kowaluk; correct?

13 A. It would appear to be, and I do, I think,

14 remember writing this sort of e-mail.

15 Q. Now, the very first item under that is:

16 Given the results of phase

17 IIb, what is the value of the

18 currently identified backups; i.e.

19 go to backup, proceed with 594 and

20 start back upset, et cetera. Can we

21 steal these analyses from the SDG

22 project two years ago, question mark.

23 Do you see that?

24 A. Yes.

25 Q. What results of the phase IIb study were you

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 referring to here?

2 A. I believe in this context I'm referring to --

3 and this is the scope and frame discussion for

4 planning. I believe this was referencing the

5 future state of the results.

6 So if I remember the situation

7 correctly, we left the discussion with

8 management with a focus on getting through the

9 analysis of the 114 results, and we were

10 preparing for the decision analysis while those

11 data were being cleaned up and getting ready for

12 database release and those sorts of things, and

13 actually patients would still probably be dosing

14 at that point, and finish and then clean up the

15 data.

16 So rather than doing all the legwork of

17 creating models after we actually had the data,

18 Liz and I were setting up the decision analysis

19 framework that could ultimately then just accept

20 the results of the study and then allow a more

21 efficient process to analyze the results and the

22 decisions.

23 Q. It appears from this e-mail that you were

24 discussing the results that you then knew from

25 the phase IIb study.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 MR. PHILLIPS: Objection.

2 BY MR. DAVIS:

3 Q. And it says:

4 Given the results of phase

5 IIb.

6 My question is, what results from the

7 phase IIb study for 594 were you aware of as of

8 February 2nd, 2001?

9 A. No results.

10 Q. So is it your belief that what you are really

11 saying here is given the future results?

12 A. Yes.

13 Q. Wasn't there any discussion with Dr. Leiden

14 about the high premature termination rate?

15 A. I don't recall.

16 Q. Any discussion with him about the significant

17 number of adverse events in that trial?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: Not that I remember.

20 BY MR. DAVIS:

21 Q. Do you recall getting any negative feedback

22 regarding 594 in the course of that February

23 presentation or the presentation to Dr. Leiden?

24 MR. PHILLIPS: Objection.

25 THE WITNESS: Not that I remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 particular e-mail is ABT-594 pain DSG kick-off

2 meeting 2-22-01. Do you see that?

3 A. Yes.

4 Q. Does that lead you to believe that this was the

5 first meeting of this group?

6 MR. PHILLIPS: Objection.

7 THE WITNESS: The first meeting of

8 the -- of the group defined with that particular

9 title, though decision analysis at Abbott had

10 gone through multiple iterations with multiple

11 different named groups as they started from an

12 out-sourcing in the very first to creating an

13 internal group, and its name changed several

14 times.

15 (Marked for identification

16 Deposition Exhibit No. 40.)

17 BY MR. DAVIS:

18 Q. Dr. McCarthy, you have Exhibit 40. Would you

19 look at the document for a moment and tell me if

20 you've seen it before?

21 A. I don't think so. Not that I recall.

22 Q. This, again, appears to be a memo prepared by

23 Michael Meyer or others working with Michael

24 Meyer. This one is dated March of 2001.

25 Do you recall receiving documents like

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 this from Michael Meyer pertaining to 594 while
2 you were working on that project?
3 A. I don't -- not that I recall.
4 Q. If you take a look at the second page of this
5 exhibit under project status summary?
6 A. Yes.
7 Q. It says:
8 During the past year, the
9 project has continued to focus on a
10 mechanism-based approach to the
11 identification of compounds
12 exhibiting retention of
13 broad-spectrum analgesic activity
14 associated with ABT-594, but with an
15 improved therapeutic index relative
16 to the key adverse events, emesis,
17 nausea and dizziness, that have
18 consistently been observed during the
19 clinical evaluation of ABT-594.
20 Do you believe that that statement was
21 true as of March 2001?
22 MR. PHILLIPS: Objection.
23 THE WITNESS: I don't know about the
24 date, and consistently, I think, is an incorrect
25 statement.

1 BY MR. DAVIS:

2 Q. It goes on to say:

3 ABT-594 is currently
4 completing a phase IIb trial in
5 diabetic neuropathy at doses up to
6 four fold above the doses studied in
7 the previous neuropathic pain trial,
8 with the results from that trial
9 expected by May 2001.

10 Is that approximately the time frame
11 within which you expected the results of that
12 trial?

13 A. May 2001 seems approximately when we did get the
14 results of the study.

15 Q. It says:

16 It will be critical to the
17 continuation of the program to
18 demonstrate enhanced clinical
19 efficacy at these higher doses.

20 Do you agree with that?

21 MR. PHILLIPS: Objection.

22 THE WITNESS: No.

23 BY MR. DAVIS:

24 Q. Why not?

25 A. I don't know that the enhanced clinical

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 efficacy -- I don't know what the higher doses

2 are. I don't know why enhanced clinical

3 efficacy is linked to higher doses.

4 Q. Would you look at the page that's Bates number

5 ends in 4137. I believe it is the fifth page of

6 this memo by Dr. Meyer. Under scientific logic

7 for drug discovery background, do you see that

8 in that paragraph -- please read that whole

9 paragraph under background to yourself and tell

10 me, please, when you are done.

11 A. Yes.

12 Q. Do you agree with Dr. Meyer that the

13 dose-limiting side effects of emesis, nausea and

14 dizziness had made it difficult, at least up

15 until that point in time, to reach what Abbott

16 believed should be therapeutically relative

17 plasma concentrations of ABT-594 received to

18 achieve maximal efficacy?

19 A. No.

20 Q. Did you ever have any discussions with Dr. Meyer

21 on that point?

22 A. I would have had many discussions with Dr.

23 Meyer, but I don't recall us sharing a

24 discussion about that particular point.

25 Q. Did you believe Dr. Meyer to be reasonably

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 competent in what he did at Abbott?

2 MR. PHILLIPS: Objection.

3 THE WITNESS: It would certainly be

4 speculation for me to evaluate Mike Meyer in his

5 ability to do neuroscience drug discovery, but

6 Mike Meyer has no qualifications to interpret

7 clinical trial data or to provide expert opinion

8 on the development of -- the clinical

9 development of drugs.

10 (Marked for identification

11 Deposition Exhibit No. 41.)

12 BY MR. DAVIS:

13 Q. Dr. McCarthy, you have in front of you

14 Exhibit 41. Would you look at the document for

15 a moment and tell me if you've seen it before,

16 please.

17 A. I think I saw this yesterday.

18 Q. This is a core team meeting minutes. What core

19 team does this pertain to?

20 A. I don't know.

21 Q. You appear to be one of the attendees at a

22 meeting on March 5th, 2001. If you look at the

23 list of attendees, does that refresh your

24 recollection as to what core team is meeting?

25 A. I don't know which core team, no.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Is this the -- are these minutes of a decision

2 analysis group meeting that -- of the decision

3 analysis team that was referenced in Exhibit 39?

4 A. It could very well be.

5 Q. Do you recognize the attendees at the meeting as

6 people who were members of that decision

7 analysis team?

8 A. In part, yes.

9 Q. Just going through the attendees very quickly,

10 Nigel -- and I apologize up front, I'll butcher

11 the names, but --

12 A. Nigel Livesey.

13 Q. Livesey. Who is Nigel Livesey?

14 A. He was from regulatory affairs, and his function

15 was to represent the Abbott international

16 regulatory perspective.

17 Q. And then who is Laura Robinson?

18 A. She was a representative from the new product

19 development group in marketing.

20 Q. How about Sandeep Dutta?

21 A. He was a pharmacokineticist.

22 Q. Steve Townsend?

23 A. He was the regulatory affairs representative

24 representing the U.S. pharmaceutical

25 perspective.

1 A. No.

2 Q. So just so the record is clear, you have no
3 reason to believe that that date is inaccurate?

4 A. Yes. Wait. Sorry.

5 Q. What I said was correct, you have no reason to
6 believe that that date is inaccurate?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: I'm sorry, I do have
9 reason to believe it's inaccurate, because I
10 don't remember the meeting.

11 BY MR. DAVIS:

12 Q. Aside from the fact that you don't remember it,
13 do you have any reason to believe that the date
14 listed on this document is inaccurate?

15 A. No reason other than I don't remember.

16 Q. Going back to the first bullet point there, did
17 you believe or understand that the tolerability
18 of ABT-594 needed to be improved as of early
19 March 2001?

20 A. To the best of my knowledge, the -- from the
21 information we reviewed, the unblinded
22 information from the study wasn't available
23 until May, so I would have had -- before that
24 time, I would have had no basis for knowing that
25 the tolerability should be improved.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 problems or issues with 594 that needed to be
2 addressed in order to make it a commercially
3 viable product?

4 A. I didn't know.

5 Q. Is that something that you were investigating at
6 that point in time?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: Well, other than through
9 the already initiated 114 trial.

10 BY MR. DAVIS:

11 Q. I guess my question is other than the 114 trial,
12 were you doing anything to investigate a link
13 between 594 and emesis or trying to determine
14 whether there was something that could be done
15 to eliminate any emesis liability associated
16 with 594?

17 A. I was not.

18 (Marked for identification
19 Deposition Exhibit No. 42.)

20 BY MR. DAVIS:

21 Q. I show you what's been marked as Exhibit 42.
22 Dr. McCarthy, I ask you to look at this document
23 and tell me if you've seen it before.

24 A. I believe I saw it yesterday, or at least parts
25 of the document look familiar.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Did you participate in the creation of this
2 document?

3 A. I participated in the creation of -- certainly
4 certain slides look familiar to the extent that
5 I know that I participated in their creation,
6 yes, but not all.

7 Q. Do you recall participating in an Abbott
8 portfolio review in or about March 7 to 9, 2001?

9 A. I do not.

10 Q. Do you recall that in the late 2000, early 2001
11 time frame, Abbott was engaged in a transaction
12 whereby it acquired Knoll Pharmaceuticals?

13 A. Oh, I don't remember the dates of the Knoll
14 acquisition.

15 Q. Do you recall that at some point in time Abbott
16 acquired Knoll Pharmaceuticals?

17 A. Yes.

18 Q. Do you recall that Abbott conducted a review of
19 its portfolio and the Knoll portfolio in the
20 aftermath of that transaction?

21 A. Yes.

22 Q. Did you participate in any way in that review?

23 A. I believe I did.

24 Q. Did you participate by making any presentations?

25 A. I believe I did.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Did you make any presentations concerning 594?

2 A. I don't remember.

3 Q. The presentations that you recall making in the

4 course of that review, to whom were the

5 presentations made?

6 A. It was a broad group of management at Abbott.

7 That's all I remember.

8 Q. Do you recall specifically any of the attendees?

9 A. Oh, not specifically, no.

10 Q. Was Dr. Leiden an attendee?

11 A. I can't remember if he was or not.

12 Q. Dr. Silber?

13 A. I don't think so.

14 Q. Perry Nisen?

15 A. I don't remember.

16 Q. Were other compounds reviewed at the same time?

17 A. I believe so, yes.

18 Q. Did you sit in while other compound --

19 presentations were made with respect to other

20 compounds?

21 A. Not to my recollection.

22 Q. And as you sit here today, do you believe that

23 the presentation materials we see that have been

24 marked as Exhibit 42 are your presentations

25 materials from that portfolio review?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. They could have been the -- I remember these --
2 the two little lines being something borrowed
3 from the Knoll style, and during that time
4 everyone seemed to be trying to use these. It's
5 a blue and a light blue. So these could have
6 well been from that overview, but it also
7 happened that that slide format started getting
8 used quite a bit for a long time after that. So
9 I can't -- it doesn't help me to place when it
10 actually happened.

11 Q. If you look at the lower left-hand corner --
12 it's sometimes difficult to read these -- do you
13 see a reference to Knoll presentation?

14 A. Yes.

15 Q. So again, does that refresh your recollection as
16 to whether this was a presentation you made in
17 that context?

18 A. That would seem consistent with that.

19 Q. Now, if you look at the page that's Bates number
20 ends in 7535, there is an ABT-594 targeted
21 product profile. Do you see that?

22 A. Yes.

23 Q. What is a targeted product profile?

24 A. A target product profile is an ideal set of
25 attributes for a compound against which the

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 emerging actual characteristics of the drug are
2 compared to.

3 Q. If you look at this particular targeted profile,
4 it says -- do I read it correctly that one of
5 the targeted characteristics was less than 20
6 percent nausea, vomiting, dizziness?

7 A. I think that's a correct interpretation.

8 Q. Up to this point in time, had that target been
9 met with respect to 594?

10 A. I don't know.

11 Q. Would you look, please, at the page that's Bates
12 number ends in 7550. There is a reference there
13 to:

14 ABT-594 summary of phase IIb
15 plans.

16 One of them is the neuropathic pain
17 study. That is the 114 study; correct?

18 A. Yes.

19 Q. And again, it says data available 5-2001. What
20 data was that?

21 A. I don't know what this specifically meant. I
22 can only infer that that is the unblinded
23 results of the study would be available in
24 May 2001.

25 Q. Further down it says tolerability evaluation.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 What is that a reference to?

2 A. I'm not sure.

3 Q. Was part of the phase IIb objective to do a
4 tolerability evaluation of 594?

5 A. It might have been. I don't remember at this
6 point.

7 Q. If you look a few more pages into this document,
8 the page that Bates number ends in 7553, when
9 did you last see this page?

10 A. I'm sorry, say again.

11 Q. When did you last see this page?

12 A. Oh, I do not know.

13 Q. The very first bullet point has potential issues
14 slash threats slash negatives. Do you see that?

15 A. Yes.

16 Q. And the first item is:

17 Tolerability issues.

18 Nausea, vomiting, dizziness.

19 As of the date of this presentation,
20 did you regard those as issues, threats or
21 negatives associated with 594?

22 MR. PHILLIPS: Objection.

23 THE WITNESS: I don't know.

24 BY MR. DAVIS:

25 Q. Would you have listed them under potential

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 issues, threats or negatives if you didn't

2 regard them as applying to one of those

3 categories?

4 MR. PHILLIPS: Objection.

5 THE WITNESS: No.

6 BY MR. DAVIS:

7 Q. Do you recall any discussion around the

8 tolerability issues during the course of this

9 presentation?

10 A. No.

11 Q. The tolerability issues that you reference here,

12 were those tolerability issues that were

13 encountered in any way in the course of 114

14 trial?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: Well, in the sense that

17 in -- as to this point we know what the issues

18 were from the outcome of the trial. I'm not

19 sure -- I don't think I'm answering your

20 question.

21 BY MR. DAVIS:

22 Q. Well, I guess were you -- did you have in mind

23 at the time that you were making this

24 presentation any tolerability issues that had

25 been encountered in the 114 trial?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. Not that we knew were related to 594.

2 Q. You knew there had been tolerability issues

3 during the course of that trial?

4 MR. PHILLIPS: Objection.

5 THE WITNESS: Yes.

6 BY MR. DAVIS:

7 Q. And adverse events associated with nausea,

8 vomiting and dizziness?

9 A. Yes.

10 Q. At that point in time you just didn't have the

11 unblinded data; correct?

12 A. Correct.

13 (Marked for identification

14 Deposition Exhibit No. 43.)

15 BY MR. DAVIS:

16 Q. Dr. McCarthy, when did you last see this

17 document?

18 A. Oh, I don't recall.

19 Q. If you take a look, there seems to be a

20 calendar, maybe an electronic calendar entry and

21 then an agenda for a meeting scheduled for

22 Monday the 12th of March 2001. Do you see that?

23 A. Yes.

24 Q. Did you see -- have you seen this document?

25 A. I think I might have seen it yesterday.

1 Q. Who was Paul Andrews, Ph.D.?

2 A. If I remember, he is a researcher who is an

3 expert on gastrointestinal disease, in

4 particular with respect to animal models of

5 emesis.

6 Q. Now, is this a meeting that you scheduled?

7 A. I can't remember. I can't remember if I did or

8 the discovery folks did.

9 Q. It says on the first page that:

10 Paul Andrews, Ph.D. will be

11 joining us for a discussion of

12 ABT-594's tolerability issues,

13 especially the emetic liability.

14 Do you recall this discussion?

15 A. I do recall the discussion, that it occurred,

16 yes.

17 Q. Did Abbott invite Dr. Andrews to come to talk

18 about 594?

19 A. No.

20 Q. How did it come about that a meeting was

21 scheduled in which Dr. Andrews would speak on

22 ABT-594's tolerability issues?

23 A. We invited Dr. Andrews to talk about animal

24 models of emesis, and I don't recall if we sent

25 him any information on 594 or what we asked him

1 to do to comment on 594 at this point.

2 Q. Would you look at the agenda on the next page.

3 It's titled -- underneath the date it says

4 ABT-594 discussion, and it lists you among the

5 attendees. Do you see that?

6 A. Yes.

7 Q. And the first area, subject area is ABT-594

8 review, preclinical data and clinical data. Do

9 you see that?

10 A. Yes.

11 Q. And from 10:00 to 11:00 a.m. was scheduled a

12 presentation from Dr. Andrews regarding the

13 mechanisms of ABT-594 induced emesis?

14 A. Yes.

15 Q. Does this refresh your recollection on whether

16 Dr. Andrews was asked to come and comment on

17 mechanisms of ABT-594 induced emesis?

18 A. It doesn't, because my recollection is that Dr.

19 Andrews talked about mechanisms of emesis in

20 general, and I don't remember -- certainly I

21 remember the meeting. I remember, as this

22 agenda suggests, that there was a preface

23 component where 594 was discussed, and given Dr.

24 Andrew's focus on preclinical models, it was

25 predominantly Mike Meyer, but I remember just

1 dimly that Dr. Andrews predominantly talked
2 about pathways of emesis in preclinical models
3 more than anything.

4 Q. Would it be fair to say that your interest and
5 Abbott's interest in speaking to Dr. Andrews at
6 that point in time was focused on 594?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: No.

9 BY MR. DAVIS:

10 Q. So all the references here to ABT-594 discussion
11 and ABT-594 review and mechanisms of ABT-594
12 induced emesis, that doesn't mean that the
13 interest in this meeting was focused on 594?

14 A. That's correct.

15 MR. PHILLIPS: Objection. The
16 skepticism in your voice and your expression,
17 Counsel, is not particularly appreciated and I
18 think is inappropriate.

19 MR. DAVIS: Do not at any point in time
20 correct me with respect to the tone of my voice
21 or skepticism expressed in my questions. That
22 is not your place, Counselor. That is not an
23 appropriate objection. Don't make them.

24 MR. PHILLIPS: Don't lecture me, Mr.
25 Davis. I told you that yesterday, and I'll tell

1 you that again today.

2 MR. DAVIS: Mr. Phillips, that was
3 called for, you got exactly what you deserve;
4 please do not instruct me on how to run my
5 deposition.

6 MR. PHILLIPS: Okay. Don't instruct me
7 as to what objections to make or what comments
8 to make, Mr. Davis. My comment stands on the
9 record.

10 MR. DAVIS: You know that that
11 objection is inappropriate. Don't make them.

12 MR. PHILLIPS: I do not know that.

13 BY MR. DAVIS:

14 Q. Did this particular meeting have anything to do
15 with 594?

16 A. I'm sure 594 was discussed.

17 Q. Was it focused in any way on 594?

18 A. My recollection is that it was less focused on
19 594 and more focused on preclinical models that
20 could be used to further understand emetic
21 liability with NNRs.

22 Q. Did you -- at the point in time that this
23 meeting was scheduled, did you have a belief
24 that there was a need to investigate further
25 tolerability issues, particularly emesis issues,

1 pertaining to 594?

2 A. Yes.

3 Q. Why?

4 A. Because since 1997 we knew that 594 was

5 associated with nausea, vomiting and dizziness.

6 Q. Had you seen anything in the preliminary results

7 of the 114 study as of early March 2001 that led

8 you to believe that 594 did not have continued

9 tolerability issues?

10 A. To my knowledge, there were no preliminary

11 results from 114. There was only the results --

12 the final results.

13 Q. Had you seen anything in the adverse event data

14 or the premature termination data from the 114

15 study prior to this meeting that led you to

16 believe that 594 did not continue to suffer from

17 tolerability issues?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: No.

20 BY MR. DAVIS:

21 Q. Did you see anything in that data that you

22 thought tended to confirm or tended to

23 demonstrate more likely than not that 594

24 continued to have tolerability issues?

25 MR. PHILLIPS: Objection.

1 THE WITNESS: No.

2 BY MR. DAVIS:

3 Q. You didn't draw any conclusions one way or the

4 other from the number of adverse events

5 involving nausea and vomiting in that trial

6 before the data was unblinded?

7 A. I did not.

8 Q. And did the data that you had received regarding

9 adverse events and premature terminations from

10 the 114 trial prior to March 12, 2001 play any

11 role in Abbott's decision to speak to Dr.

12 Andrews about emetic liability associated with

13 594 or NNRs?

14 A. Not that I was aware of.

15 Q. Who specifically made the arrangements for the

16 meeting with Dr. Andrews?

17 A. I don't know. I believe Marleen Verlinden knew

18 Paul Andrews, because Marleen's drug development

19 experience had been predominantly in disorders

20 of reflux from her time at Janssen, so she had

21 an extensive network of relationships, and so it

22 was likely -- I believe she knew Dr. Andrews

23 personally and was likely the one who set it up.

24 I don't have a specific recollection that I did.

25 Q. Did Dr. Andrews actually make a presentation

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 during the course of this meeting?

2 A. Yes.

3 Q. Did he use slides?

4 A. I believe so.

5 Q. Did he give copies of those slides to anyone at

6 Abbott?

7 A. I don't remember.

8 Q. Where did this meeting take place?

9 A. I have the distinct recollection that it

10 happened in AP34 in a room facing south on maybe

11 the third or fourth floor in a conference room.

12 Oddly, I can almost remember it.

13 Q. And was the presentation made by Dr. Andrews --

14 was it a PowerPoint presentation?

15 A. I don't remember.

16 Q. Were there handouts?

17 A. I don't remember.

18 Q. Was the presentation recorded in any way?

19 A. No.

20 Q. Did anybody participate in the presentation via

21 telephone or via some other electronic link?

22 A. Not that I remember.

23 Q. What do you recall Dr. Andrews had to say in the

24 course of the presentation about mechanisms of

25 ABT-594 induced emesis?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 MR. PHILLIPS: Objection.

2 THE WITNESS: I don't remember. I

3 remember -- the part that I remember is being

4 moderately lost in his description, which seemed

5 relatively generic, to pathways of emesis

6 preclinically, and not particularly helpful or

7 specific to NNRs.

8 (Marked for identification

9 Deposition Exhibit No. 44.)

10 BY MR. DAVIS:

11 Q. Dr. McCarthy, you have what's been marked as

12 Exhibit 44. I'd ask you to look at the document

13 and tell me if you've seen it before.

14 A. Not this one, to my recollection.

15 Q. It appears to be an e-mail from Ms. Kowaluk to

16 you, among others, dated March 27th, 2001

17 concerning the ABT-594 pain DSG core team. The

18 fourth paragraph down of the e-mail says:

19 We will be taking a brief

20 hiatus from the DSG analysis for

21 about a month while some members of

22 the team participate in pulling

23 together a review for the R&D

24 strategy off-site called by Jeff

25 Leiden for the first week of May.

1 A. No.

2 Q. If you take a look at the page titled -- page

3 number 8:

4 Table of contents of issues

5 to consider and/or present at the

6 retreat.

7 Does that look familiar to you?

8 A. No.

9 Q. So none of this is causing you to have a

10 refreshed recollection regarding participation

11 in either preparation or presentations at this

12 retreat?

13 A. No. I can remember generically review sessions

14 of various sorts with Jeff, but I can't remember

15 this one in particular. They all blur together.

16 Q. Did any of those review sessions have to do with

17 594?

18 A. Off site, I don't remember that they did.

19 Q. Do you remember review sessions on site

20 regarding 594?

21 A. Yes.

22 Q. With Leiden?

23 A. Yes.

24 Q. Do you recall any feedback ever received from

25 Jeff Leiden concerning 594?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. Yes, two instances, one when we had the results
2 of the 114 study, and it was -- I remember Jeff
3 was there. I remember John was there. I don't
4 remember who else was there, John Leiden, and --

5 Q. You said John Leiden. Did you mean John
6 Leonard?

7 A. Sorry, John Leonard and Jeff Leiden, and I think
8 there were just a few other people there, and we
9 were talking about the results of the study, and
10 he had asked that we consider how -- if we could
11 still make the trade off between efficacy and
12 side effects work at intermediate doses. And
13 that led to another intensive effort of thinking
14 to make those intermediate doses work, which
15 resulted in a kind of final recommendation or
16 discussion with -- I believe with Jeff, and the
17 decision to stop development. But those are
18 really the only things I remember about
19 interaction with Jeff on 594.

20 Q. The unblinded results for the 114 study, were
21 they adverse in any way?

22 MR. PHILLIPS: Objection.

23 THE WITNESS: I don't know the
24 definition -- what do you mean by adverse?

25 BY MR. DAVIS:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. What did you perceive to be the results of the
2 study after they were unblinded? Good,
3 positive, negative, somewhere in between?

4 A. Somewhere in between.

5 Q. More positive than negative? Vice versa?

6 A. I would say as much of one as the other.

7 Q. What were the aspects of the unblinded results
8 that you thought were negative?

9 A. I'm sorry, I was answering the question before
10 about the -- I'm sorry, the unblinded. The
11 portions of the unblinded results that were
12 negative were that there was not -- it did not
13 appear to be that there was a dose at which
14 there was an appealing balance between the
15 benefit of the drug and the nausea, vomiting and
16 dizziness.

17 Q. Did you regard that as a significant negative?

18 MR. PHILLIPS: Objection.

19 THE WITNESS: I saw that as certainly a
20 very unlikely -- sorry. I interpreted that to
21 mean that the utility of further developing the
22 drug was pretty low.

23 BY MR. DAVIS:

24 Q. Is it fair to say that after the results of the
25 114 study were unblinded and you looked at those

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 results, you believed that it was less -- it was
2 more likely than not that 594 would not be
3 further developed?

4 A. Yes.

5 Q. Was it the nausea, vomiting and dizziness that
6 caused to you think that?

7 A. It was the interrelationship of the efficacy and
8 the nausea, vomiting and dizziness.

9 Q. When you say the interrelationship, meaning that
10 you didn't think that the efficacy was so great
11 as to offset the nausea, vomiting and dizziness
12 that was observed in the trial?

13 A. That's correct.

14 Q. Going into the 114 trial, did you understand 594
15 to be efficacious?

16 A. I believed it was.

17 Q. Did you have data to that effect?

18 A. I believed that -- I interpreted the data that
19 we had available at the time to feel confident
20 enough to recommend that we should invest in a
21 study like 114 to further evaluate the efficacy.

22 Q. Do you still believe that 594 is efficacious?

23 A. With the 114 data, I do believe that the drug is
24 efficacious.

25 (Marked for identification)

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Deposition Exhibit No. 46.)

2 BY MR. DAVIS:

3 Q. Dr. McCarthy, I'll show you what's been marked

4 as Exhibit 46 and ask you if you've seen this

5 document or a document in this format before.

6 A. I've seen documents in this format.

7 Q. Have you seen this one in particular before?

8 A. I don't recall.

9 Q. The documents that you saw in this format, how

10 did it come about that you received them?

11 A. The first part I would receive at various times.

12 I believe they had something more to do with

13 budget cycle planning, and summarized from a

14 portfolio level, they were intended to be

15 one-page summaries of the portfolio analysis.

16 The other pages look like the typical monthly

17 status update pages.

18 Q. Did you contribute to the creation of these

19 documents, to your knowledge?

20 A. My contribution to the first page was small and

21 indirect in that, you know, about at annual

22 intervals we would develop budgets which

23 contributed to, for example, development costs.

24 And on the other pages, the monthly update,

25 there were components that I would contribute

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 updates as appropriate to, you know, my area of
2 clinical --

3 Q. If you would look at the second page of
4 Exhibit 46, please, under monthly highlights,
5 the one and only bullet point states:
6 Blind broken on April 20 for
7 M99-114 painful diabetic neuropathy
8 Phase IIb study.
9 Do you see that?

10 A. Yes.

11 Q. What do you understand that to mean?

12 A. That would mean that the database had been
13 locked and the blind had been broken and that
14 sometime after April 20th the data would become
15 available for review.

16 Q. Did you receive notification when the database
17 was locked?

18 A. Yes, I believe I would have, yes.

19 Q. How long before the study results were unblinded
20 was the database locked?

21 A. I don't remember.

22 Q. Did you receive the data as soon as it was
23 unblinded?

24 A. No. The statisticians will often print out for
25 their purposes to make sure that the unblinding

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. I can't remember a specific instance, but I can
2 imagine -- I can remember that from time to time
3 the statisticians would send pieces of data in
4 text format in an e-mail, but not data in the
5 sense of a database.

6 Q. Did you, for example, ever take any data and
7 manipulate it in the form of a spreadsheet or
8 the like?

9 A. Not that I recall. I mean I guess to be
10 literally true, the PowerPoint graph generator
11 does use Excel spreadsheet function. So you are
12 effectively entering that data into a
13 spreadsheet to display a graphic, but not to
14 develop -- to analyze the data.

15 Any data analysis is done through the
16 statisticians using their SAS database, because
17 that would be -- that's a validated database.
18 Excel isn't valid for the purposes of analyzing
19 data.

20 Q. The April 20th date listed on Exhibit 46 for the
21 unblinding of the data for the 114 study, is
22 that consistent with your recollection of the
23 approximate date in which it was unblinded?

24 A. Generally, yes.

25 Q. Do you recall the data being unblinded earlier

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 than anticipated?

2 A. No.

3 Q. Some of the documents that we've seen indicate
4 that the data was expected in May of 2001.

5 A. I think you used the word unexpected. There is
6 usually poor -- we're usually generally pretty
7 poor at estimating when it's actually going to
8 get done. Plus or minus a month is not unusual.

9 (Marked for identification
10 Deposition Exhibit No. 47.)

11 BY MR. DAVIS:

12 Q. Dr. McCarthy, I have Exhibit 47. Would you look
13 at the document for a moment and tell me if you
14 have seen it before?

15 A. Not this document.

16 Q. Did you participate in the preparation of this
17 document, to your knowledge?

18 A. The slides here all look familiar to me as
19 slides I created.

20 Q. You think you did create the --

21 A. Yes, each -- let me just verify that each and
22 every one of these looks like slides that I
23 created or my assistant created with my
24 oversight. Yes.

25 Q. So these were created -- the date is 4-23-01

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 which is, according to the date on Exhibit 46,
2 about three days after the data was unblinded.

3 For what purpose did you actually
4 create these slides?

5 A. In the period immediately after the blind was
6 broken and initial results are seen, as we
7 talked about before, for any clinical trial
8 there is great interest in knowing what the data
9 is.

10 So, you know, at every level of the
11 company -- well, that is going too far.

12 Certainly at my manager's level and their
13 manager's level there is great interest, keen
14 interest to know what the results of the study
15 are.

16 So a kind of very quick, you know,
17 short, pithy presentation or other communication
18 document is usually presented to communicate
19 those results.

20 Q. The slides, beginning in the second slide, in
21 the lower left-hand corner, referenced the
22 4-23-01 preliminary data. You had the final
23 study data at that point in time; correct?

24 A. Yes. In this context preliminary data usually
25 referenced anything up to the time as those data

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 used to populate the clinical study report

2 that's signed off.

3 Q. I'm sorry, would you repeat that?

4 A. So because the final clinical study report, the

5 data in that document will form the basis of

6 regulatory submissions, that -- those data for

7 submissions represent in -- from the perspective

8 of companies as final data. Anything, even

9 after the database is locked, and that point of

10 those final effectively sealed data points are

11 considered, you know, preliminary.

12 Q. So by preliminary data, you don't mean that you

13 have something less than the final locked data?

14 MR. PHILLIPS: Objection.

15 THE WITNESS: This would be something

16 less than the -- not less. This could

17 potentially be -- the reason that that caveat is

18 put there is that this may not match to the last

19 digit the data in the clinical study, the

20 ultimate clinical study report.

21 BY MR. DAVIS:

22 Q. At the time you prepared this, the data had been

23 locked; correct?

24 A. Yes.

25 Q. So at the time the data is locked, is it final?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 case, that there were multiple locked databases?

2 A. I don't recall, but I wouldn't generally be

3 informed of that or I wouldn't necessarily pay

4 attention to it. It's the statisticians and

5 data management that keep track of those.

6 Q. Would you look at the last page, please, of this

7 presentation. I'm sorry, you may have answered

8 this. Do you recall to whom you made this

9 presentation?

10 A. I remember that one of the first people I

11 presented it to was Marleen Verlinden and John

12 Leonard.

13 Q. Anybody else?

14 A. Not that I remember.

15 Q. Did you understand them to be one of -- some of

16 the people who were eager to get the

17 information?

18 A. Yes.

19 Q. The very last page here is a slide that

20 addresses adverse events among the different

21 dosing levels; correct?

22 A. Yes.

23 Q. Just so I understand the data here correctly, do

24 I interpret this correctly if I read it that,

25 for example, under nausea, that 46 percent of

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 the participants in the study reported nausea

2 with a 300 microgram dose of ABT-594?

3 A. That's correct.

4 Q. And then vomiting was experienced by 21 percent

5 of the patients who received that dosing?

6 A. That's correct.

7 Q. And 25 percent of the patients who received the

8 225 microgram dose of 594 experienced vomiting;

9 is that right?

10 A. Yes.

11 Q. Is it true that from this data you concluded

12 that these dosing levels were associated with a

13 dose-dependent increase in nausea, vomiting and

14 dizziness?

15 A. Generally.

16 Q. Had you suspected that earlier?

17 A. Well, in all previous trials there was a

18 dose-dependent increase in nausea, vomiting and

19 dizziness.

20 Q. And did you suspect that that was going to be

21 the outcome here when you saw the adverse events

22 and the premature terminations?

23 A. I don't think that information modulated the

24 expectation that in all future trials nausea,

25 vomiting and dizziness would continue to be

1 dose-dependent.

2 Q. Maybe you answered my question, I'm not sure.

3 My question is, did you suspect that that would

4 be the case after you saw the adverse event

5 information and preliminary termination

6 information for the 114 trial?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: Yes. It was also true

9 that I suspected that before I saw that.

10 BY MR. DAVIS:

11 Q. The unblinded data?

12 A. Before I saw the blinded dropout information.

13 Q. I want to make it clear. The data we were just

14 looking at and the dose-dependent relationship

15 between nausea, vomiting and dizziness between

16 594 and those adverse events, is this something

17 that you suspected before the unblinding of the

18 data from 114?

19 MR. PHILLIPS: Objection.

20 THE WITNESS: Yes, I suspected the dose

21 response nature of the adverse events.

22 BY MR. DAVIS:

23 Q. Did any of the information that you received

24 before -- about the 114 trial before the

25 unblinding of that trial further your suspicions

1 in that regard?

2 A. I don't think so.

3 (Marked for identification

4 Deposition Exhibit No. 48.)

5 BY MR. DAVIS:

6 Q. Dr. McCarthy, I show you what's been marked as

7 Exhibit 48 at your deposition and ask you to

8 take a look at it for a moment and tell me if

9 you can identify it for me, please.

10 A. It looks to be the clinical study report for

11 study M99-144.

12 Q. Can you tell whether this is the final report?

13 A. I cannot.

14 Q. If it was a draft report would it be stamped

15 draft somewhere?

16 A. I don't remember what the Abbott system was, to

17 be honest.

18 Q. I can represent to you that we've checked, and

19 this is the last version of this report that we

20 have.

21 A. Okay.

22 Q. If there were further versions of it, would you

23 expect that they would be in Abbott's file

24 somewhere? If there was a final version and

25 this was a draft, would you expect that the

1 final version would be in Abbott's files?

2 A. Yes.

3 Q. This one is dated the 6th of July 2001. Is that

4 consistent with your recollection of the time

5 frame in which a final clinical study report was

6 prepared for the 114 trial?

7 A. It seems a reasonable assumption.

8 Q. Did you actually review this report before it

9 was finalized?

10 A. I don't know if I -- since I don't know which

11 version this is, I can't say if I reviewed this

12 particular one, but I would have been

13 responsible for reviewing the drafts and the

14 final report.

15 Q. Did you review the entire report?

16 A. Yes, I would have had accountability for the

17 entire report.

18 Q. Would you have identified and sought to correct

19 any errors that you found in the report?

20 A. Yes. And to some extent, that's a shared

21 effort. The statistician has the accountability

22 of QC'ing all of the data points, so I would not

23 have checked every data point. My colleagues in

24 statistics would have done that.

25 Q. Do you recall at some point in time finalizing

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 this report?

2 A. I don't remember.

3 Q. Do you recall signing a copy of the report?

4 A. I don't remember.

5 Q. To whom was the report sent or issued?

6 A. When a report is final, it's warehoused for

7 future use in submissions, if there is a

8 submission.

9 Q. In reviewing the information in the report, did

10 you attempt to confirm or assure that it was as

11 accurate as possible?

12 A. Yes.

13 Q. Would you turn, please, to the page that's Bates

14 numbered 8639, last four digits.

15 A. 8639?

16 Q. Correct.

17 A. Yep.

18 Q. There is a section there titled 9.8:

19 Changes in the conduct of

20 the study or planned analyses.

21 Do you see that?

22 A. Yes.

23 Q. By the way, when is the last time you saw this

24 report?

25 A. I do not remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. If you take a look at this particular page under
2 9.8.1, it says protocol changes, and it says:
3 Significant changes in the
4 developmental strategy of ABT-594
5 resulted in the study being
6 prematurely discontinued by the
7 sponsor.

8 Did I read that correctly?

9 A. Yes.

10 Q. What were the significant changes in the
11 developmental strategy of ABT-594?

12 A. I don't know. I don't know.

13 Q. Who would know?

14 A. I don't know that either.

15 Q. Well, do you recall that the decision to
16 prematurely end the enrollment for -- or to
17 prematurely discontinue the 114 study was
18 attributable to a significant change in the
19 development strategy?

20 MR. PHILLIPS: Objection.

21 THE WITNESS: I don't know what the
22 reference development strategy is.

23 BY MR. DAVIS:

24 Q. Who wrote this section?

25 A. I don't know. I can't recall.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Who else participated -- did you actually author
2 portions of this report?

3 A. I would have, yes.

4 Q. Did you author this portion?

5 A. I don't know. It would surprise me if I did.

6 This section tends to be a summary of the, as it
7 says, protocol changes, which are often tracked
8 by the project manager. The contributions of
9 the clinician tend to be in the safety sections,
10 the efficacy section and the overall
11 conclusions. This portion tends to be written
12 by the project manager.

13 Q. Who was the project manager here?

14 A. Marilyn Collicott.

15 Q. I can tell you I met her two days ago, and she
16 disclaims any authorship of this section.

17 Do you have any other understanding as
18 to who would have written this section?

19 A. No.

20 Q. Do you agree that the 114 study was prematurely
21 discontinued by Abbott?

22 A. Yes.

23 Q. You recall reviewing this section in going over
24 this final report?

25 A. No.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. If you believed that this statement was
2 inaccurate at the time that the report was
3 finalized, I assume you would have corrected it;
4 is that right?

5 A. Yes.

6 Q. Do you believe that it's inaccurate, as you sit
7 here today?

8 A. Well, I don't know what the reference
9 development strategy is meant to refer to.

10 Q. If you were trying to determine what it referred
11 to, where would you go for that information
12 within Abbott?

13 A. I do not know.

14 Q. Did you share copies of this final report with
15 any senior management at Abbott?

16 A. No. Reports generally don't go to anyone
17 senior, even when they are finalized. They are
18 intended to be documentation of a study
19 ultimately going to regulatory agencies and not
20 as an in-house reporting mechanism, internal
21 reporting mechanism.

22 Q. Prior to the premature discontinuation of the
23 114 study, did you have any discussions or
24 communications with anyone at Abbott which led
25 you to believe that Abbott was losing enthusiasm

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 for further funding or development of 594?

2 A. No.

3 Q. Are you aware of any changes in the development

4 strategy of ABT-594 that resulted in the

5 study -- the 114 study being prematurely

6 discontinued by Abbott?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: No, I don't think I am.

9 BY MR. DAVIS:

10 Q. So whatever this statement is referring to, it's

11 not anything you are aware of?

12 A. It is completely unclear to me.

13 (Marked for identification

14 Deposition Exhibit No. 49.)

15 BY MR. DAVIS:

16 Q. Would you look at Exhibit 49 for a moment, Dr.

17 McCarthy, and tell me if you've seen it before.

18 A. It seems generally familiar, but I can't -- no,

19 I don't know that I've seen it before. I can't

20 recall.

21 Q. There is a reference -- there is an e-mail at

22 the bottom here from you to Liz and Rose. Liz

23 is Liz Kowaluk; right?

24 A. Yes.

25 Q. And Rose is Rosemarie Waleska?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. No. I saw the earlier attempts to understand
2 why enrollment was slow and the early estimate
3 of discontinuations, but after that I don't know
4 that we continued to track the information.

5 Q. Did you think the dropout rate in the 114 study
6 was high before the data was unblinded?

7 MR. PHILLIPS: Objection.

8 THE WITNESS: I don't think I had a
9 strong opinion about it.

10 BY MR. DAVIS:

11 Q. Did you have any opinion?

12 A. No.

13 Q. Did you think that the adverse events were high
14 before the study was unblinded?

15 MR. PHILLIPS: Objection.

16 THE WITNESS: I had no insight into the
17 adverse events.

18 BY MR. DAVIS:

19 Q. It says:

20 PK data are not yet
21 available to allow full
22 interpretation.

23 What are PK data?

24 A. Effectively blood levels of the drug in the
25 study.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Why was that data not yet available?

2 A. It usually takes longer than the safety and

3 efficacy data to analyze and interpret.

4 Q. It says:

5 There seems to be a

6 consensus in the team that the

7 compound cannot go forward as is.

8 Do you agree that there was a consensus

9 in the DSG team at that point in time that 594

10 could not go forward as is?

11 A. Yes.

12 Q. Did some members of the team ever express that

13 view before the data was unblinded?

14 A. I don't think so.

15 Q. You never heard any discussion to that effect?

16 A. No, not that I remember.

17 (Marked for identification

18 Deposition Exhibit No. 51.)

19 BY MR. DAVIS:

20 Q. Dr. McCarthy, would you look at Exhibit 51,

21 please, and tell me if you've seen it before.

22 A. I think so.

23 Q. When did you last see it?

24 A. I'm not sure.

25 Q. Do you recall discussions about possible

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 out-licensing of ABT-259 and/or 594 in May of
2 2001?

3 A. Can you ask that question again?

4 Q. Sure. Do you recall any discussions about
5 potentially out-licensing either ABT-259 or 594
6 in May of 2001?

7 A. Not specifically. I don't recollect specific to
8 May or when it was.

9 Q. Do you recall generally discussions in the first
10 half of 2001 about potentially out-licensing
11 594?

12 A. Not that I remember in the first half.

13 Q. In the second half you do?

14 A. I have a stronger sense that once we had decided
15 not to take the drug forward, there were
16 discussions about the drug and backups in a
17 variety of ways.

18 Q. Who is Kevin Constable?

19 A. He is a member of the licensing group -- was a
20 member of the licensing group at Abbott, had
21 kind a of technical review function.

22 Q. Had you dealt with him before?

23 A. Yes.

24 Q. Had you ever dealt with him before with respect
25 to 594?

1 A. I don't think so.

2 (Marked for identification

3 Deposition Exhibit No. 52.)

4 BY MR. DAVIS:

5 Q. Dr. McCarthy, you have Exhibit 52. Would you

6 look at this document and tell me if you've seen

7 it before.

8 A. Not that I remember.

9 Q. It appears to be another monthly report

10 pertaining to 594, this one dated from July of

11 2001. If you would look at the second page of

12 the document under monthly highlights, do you

13 see a reference to:

14 Maintenance activities only.

15 Program is on hold pending global

16 pharmaceutical executive committee

17 meeting in August.

18 Do you see that?

19 A. Yes.

20 Q. When was the ABT-594 program put on hold?

21 A. I don't remember.

22 Q. Do you recall it being put on hold at some point

23 in time?

24 A. No, actually, I don't.

25 Q. Do you know what it means to put a program on

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 hold?

2 A. I don't know what the person who wrote this -- I

3 would imagine holding off starting new

4 activities.

5 (Marked for identification

6 Deposition Exhibit No. 53.)

7 BY MR. DAVIS:

8 Q. Dr. McCarthy, if you would look at Exhibit 53

9 for a moment and tell me if you've seen it

10 before.

11 A. I'm not sure that I've seen this document

12 before. I don't think so.

13 Q. It appears to be an e-mail from Ms. Kowaluk to

14 you and others dated August 16th, 2001 and

15 references:

16 ABT-594 DSG slides for PEMC

17 review.

18 You really need to know your acronyms

19 there, don't you?

20 A. Yes.

21 Q. What is PEMC?

22 A. I don't remember.

23 Q. Do you recall participating in a PEMC review of

24 ABT-594?

25 A. I don't remember PEMC. I think it is the same

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 a nausea/vomiting profile consistent
2 with first choice.

3 Is that consistent with your
4 understanding at the time?

5 A. Yes.

6 Q. And by first choice, we mean this is something
7 that a physician would respond in the first --
8 would prescribe in the first instance in the
9 event that someone presented with neuropathic
10 pain; is that right?

11 A. I believe that was the usage of the term in the
12 context here.

13 (Marked for identification
14 Deposition Exhibit No. 54.)

15 BY MR. DAVIS:

16 Q. Dr. McCarthy, you have what is marked as
17 Exhibit 54. Look at this document for a moment,
18 please, and identify it for me, if you can.

19 A. This looks like a set of slides that was either
20 used in preparation for or at a meeting to
21 summarize the senior pharmaceutical management
22 there about the results and next steps for 594.

23 Q. Did you participate in the creation of this
24 document?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Did you actually participate in the presentation
2 of this document?

3 A. There was a presentation. I don't know if this
4 is the -- was actually the version used in the
5 presentation.

6 Q. If you would turn to the third page of the
7 document, its Bates number ends in 1521, it
8 says:

9 ABT-594 August 2001 GPEC
10 review topics.

11 Do you see that?

12 A. Yes.

13 Q. And it says on the first bullet point:

14 ABT-594 efficacy in
15 neuropathic pain is significant.

16 And then a sub-bullet:

17 ABT-594 has a narrow
18 therapeutic window and efficacious
19 doses are poorly tolerated as dosed
20 currently.

21 Do you agree with that statement?

22 A. Yes.

23 Q. What is a narrow therapeutic window?

24 A. The separation of efficacy from tolerability
25 and/or safety.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. Is it fair to say that the therapeutic window is
2 the amount of dose between, at the lower end,
3 the minimum efficacious dose, and at the upper
4 end, the maximum tolerated dose?

5 A. No. The therapeutic window could refer to even
6 the effects at a specific dose, the separation
7 of safety and tolerability even within a dose.

8 Q. Can you elaborate on that? I don't understand
9 your answer.

10 A. If you had mild efficacy and moderate adverse
11 events at the same dose, you'd still infer that
12 that's a narrow therapeutic index.

13 Q. So it's more of a comparison of safety and
14 efficacy versus tolerability -- or strike that.
15 I apologize.

16 It's a comparison of safety and
17 efficacy?

18 A. Yes.

19 Q. Is there a specific formula for determining the
20 therapeutic window?

21 A. No, not that I'm aware of.

22 Q. It goes on to state in the next bullet point:

23 Decision analysis suggests

24 that the expected value --

25 Strike that. I'll go back to the prior

1 sub-point. It says:

2 Modifications to drug

3 administration have the potential to

4 improve tolerability.

5 What are you referring to?

6 A. This was the hypothesis that we had noticed

7 improved tolerability when we went from ABT-594

8 in solution to ABT-594 as a solid dosage form,

9 and there was the hypothesis that by further

10 slowing down the rate of absorption or other

11 changes to the pharmacokinetic profile with --

12 in the context of multiple dosing, that there

13 might be the possibility to further improve

14 tolerability, and I think finally I would

15 include in that bucket further experiments --

16 further adjustments to titration.

17 Q. It goes on to state:

18 Decision analysis suggests

19 that the expected value for these

20 modifications to improve tolerability

21 is small, although positive.

22 What do you mean by the expected value?

23 A. I can only infer at this point that that was

24 referencing a decision analysis that was a

25 specific expected value, expected at present

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 put together her analyses.

2 Q. Did anyone ever talk to you in the fall of 2001

3 about what they regarded as the probability of

4 success of ABT-594?

5 A. Yes, I think we continued to have discussions at

6 that point, because I think that, at least in my

7 recollection, matches the period in which we

8 were doing the -- what I called the thread the

9 needle effort to see if there was some

10 intermediate dose that could just have that --

11 just enough efficacy with adequate tolerability

12 to go forward.

13 (Marked for identification

14 Deposition Exhibit No. 56.)

15 BY MR. DAVIS:

16 Q. Dr. McCarthy, you have Exhibit 56 in front of

17 you. Would you look at this document and tell

18 me if you've seen it before.

19 A. Not that I know of.

20 Q. It appears to be a monthly status report

21 regarding ABT-594. This one is dated from

22 October of 2001. If you would look at the

23 second page of the document, please. Under

24 monthly highlights, there is only one bullet

25 point that says:

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Program is not funded for
2 2002. Out-licensing activities
3 initiated.
4 Is that consistent with your
5 recollection of the time frame within which
6 Abbott decided not to fund further development
7 of ABT-594?

8 A. Yes.

9 Q. How did you first learn of that decision?

10 A. I think we made that decision at the -- I
11 believe -- I'm quite sure it was with Jeff
12 Leiden at one of his review style meetings in
13 which Liz Kowaluk and I presented that, what I'm
14 calling the thread the needle strategy, to see
15 if we could get that just enough efficacy with
16 just the right side effects. And there was the
17 collective decision, I think, right there and
18 then, at least that's how I remember the
19 situation, that we had done everything we could
20 to figure out how to make 594 work, and we
21 decided then not to go forward.

22 (Marked for identification

23 Deposition Exhibit No. 57.)

24 BY MR. DAVIS:

25 Q. Dr. McCarthy, you have what has been marked as

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Exhibit 57. If you could look at the document
2 for a moment and tell me if you've seen it
3 before.

4 A. No, I don't think so.

5 Q. You made reference a few moments ago to a
6 meeting with Dr. Leiden and others where you
7 thought that the decision was made not to go
8 forward with funding for ABT-594. This memo
9 references an October 8th PEC meeting. Is that
10 the meeting at which that decision was made, as
11 best you recall?

12 A. I believe it was sometime in the fall, and
13 October could have been the time frame.

14 Q. Do you recall making a presentation to the PEC
15 on or about October 8th, 2001?

16 A. That seems reasonable. Again, I don't know if
17 that was the exact date, but I remember that Liz
18 and I made that final presentation in the fall.

19 (Marked for identification
20 Deposition Exhibit No. 58.)

21 BY MR. DAVIS:

22 Q. Dr. McCarthy, you have Exhibit 58 in front of
23 you. Would you look at that document for a
24 moment and tell me if you've seen it before.

25 A. I don't remember.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 meant by that. In general I think in the
2 industry it means that you put it, you know,
3 aside and effectively no one is working on it,
4 but you know there is always the chance that you
5 could come back to it some day.

6 (Marked for identification
7 Deposition Exhibit No. 59.)

8 BY MR. DAVIS:

9 Q. Dr. McCarthy, you have Exhibit 59. Would you
10 look at this document for a moment and tell me
11 if you've seen it before.

12 A. I think I have.

13 Q. When did you last see it?

14 A. I don't -- I'm losing track of all the
15 documents. I don't know.

16 Q. At the top of the first page of this document
17 there appears to be an e-mail from you to Mr.
18 Biarnesen concerning ABT-594 update. Do you see
19 that?

20 A. Yes.

21 Q. Now, if you would look near the bottom of the
22 first page and onto the top of the second page,
23 there is an e-mail from Mr. Biarnesen to a
24 variety of people with a cc to you. Do you see
25 that?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. Yes.

2 Q. Were you responding -- in your e-mail of

3 October 10th to Mr. Biarnesen, were you

4 responding to his e-mail of October 10th earlier

5 in the day?

6 A. I think I am.

7 Q. And in Mr. Biarnesen's e-mail he states:

8 Can you let me know if there

9 is any potential of out-licensing

10 this product.

11 By which he was referring to ABT-594;

12 is that right?

13 A. Yes.

14 Q. That's what you understood?

15 A. Yes.

16 Q. It says:

17 If there is, then our

18 wrap-up activities need to be

19 different than if we are strictly

20 shelving the program for good.

21 Do you see that?

22 A. Yes.

23 Q. And then you responded later the same day:

24 Mike, we will need to have a

25 discussion off-line from the main

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 project meeting, paren, doesn't need
2 to be before, close parent, at which
3 we can begin discussions of how we
4 handle ABT-594 as an asset.

5 Out-licensing 594 may have negative
6 impact upon the value of the
7 follow-ons, independent of the
8 likelihood of success of
9 out-licensing. The meeting should
10 include you, me, Danhui, Phil and
11 Jim.

12 -- did I read that correctly.

13 A. Yes.

14 Q. Who is Danhui?

15 A. I believe she was the person for new product
16 development, the marketing, commercial team.

17 Q. Phil is Phil Deemer?

18 A. Yes.

19 Q. And Jim is Jim Sullivan?

20 A. Yes.

21 Q. Who is Jim Sullivan?

22 A. He, I can't remember if it was at this time or
23 later, was the vice president of neuroscience
24 discovery.

25 Q. When you mentioned in your e-mail that

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 out-licensing 594 may have a negative impact on
2 the value of the follow-ons independent of the
3 likelihood of success of out-licensing, what did
4 you mean?

5 A. We -- I and many others felt very strongly that
6 we had a very strong proprietary position from
7 the knowledge that 594 had demonstrated
8 efficacy, something that although other
9 companies were working in the same pharmacology
10 did not yet have proof of concept. And so we
11 were worried that if others knew about the
12 efficacy that other companies would be able to
13 out-compete us in investing in the area.

14 Q. So it was a matter of -- strike that.

15 Your concern was that if you
16 out-license 594, you might be giving a
17 competitor a product that would compete with any
18 NNR product that Abbott might bring to market?

19 A. No. The licensing process itself was
20 potentially to me -- and I wasn't a
21 decision-maker about licensing -- but was
22 potentially -- might -- because it would -- even
23 under confidentiality, it would allow other
24 companies to know the state of the proof of
25 concept. So independent of whether any company

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 actually took the drug, it could diminish the
2 value.
3 Now, that wasn't my decision to make,
4 and I do remember this, that my objective here
5 was to get the people who had something to say
6 about this, and in particular Jim Sullivan, to
7 get together and talk about what were the
8 benefits and downsides of even going through the
9 licensing process.

10 Q. Did Abbott make efforts to out-license 594?

11 A. I don't know.

12 Q. Who would know that?

13 A. The folks in the licensing and development group
14 at that time, and to be honest, I can't remember
15 who was there then.

16 Q. Phil Deemer?

17 A. Well, Phil was, but he was, you know, at the
18 ground level in that group. So I don't know who
19 his management was. It's not that I don't know
20 the people, it's just that they have changed so
21 much over the years.

22 Q. Did you have that discussion with others at
23 Abbott concerning how you thought the company
24 ought to handle out-licensing of ABT-594, if at
25 all?

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 A. You know, although I remember even writing this
2 and reacting to Mike's proposal and wanting to
3 kind of get people together, I don't remember
4 the conversations that followed, and that might
5 be that maybe we never ended up having them.

6 (Marked for identification
7 Deposition Exhibit No. 60.)

8 BY MR. DAVIS:

9 Q. Dr. McCarthy, you have Exhibit 60 in front of
10 you. It appears to be an e-mail from you to Mr.
11 Deemer and a response by Mr. Deemer back to you
12 in the -- on or about October 19th, 2001. Did I
13 read that correctly?

14 A. Yes.

15 Q. You were relating to Mr. Deemer that you had
16 received a call or voice mail from a Tom Lenz at
17 Bayer inquiring about out-licensing of 594?

18 A. Yes.

19 Q. What was your understanding as to how Bayer
20 became aware of the potential for out-licensing
21 594 in that time frame?

22 A. I have no idea, which would have been the reason
23 why I promptly handed it over to licensing. I
24 think, if I remember this, I had become probably
25 associated with the clinical pain program, and

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 there was probably a general inquiry.
2 I think also around this time I was
3 posted on the Abbott People Behind the Science
4 page and identified as the analgesia person. So
5 people that might be searching the web for a
6 contact, I would start from that point on to get
7 various inquiries that were relatively germane
8 to my area, but normally would go -- you know, a
9 real licensing person at another company would
10 generally call licensing at our company.

11 Q. Do you know whether Mr. Deemer or anybody else
12 at Abbott followed up with Bayer?

13 A. I do not know.

14 Q. Did you ever receive any report back from anyone
15 at Abbott on whether someone followed up with
16 Bayer?

17 A. Not that I remember.

18 (Marked for identification
19 Deposition Exhibit No. 61.)

20 BY MR. DAVIS:

21 Q. Dr. McCarthy, I'll show you what has been marked
22 as Exhibit 61 at your deposition and ask you if
23 this is an exchange of e-mails that you had with
24 Mr. Deemer on or about October 23rd, 2001.

25 A. It looks like it, yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. If I've got this correctly, you were identifying
2 for Mr. Deemer companies that you thought might
3 be -- that Abbott might be interested in
4 soliciting to find out whether they had any
5 interest in out-licensing 594; is that right?

6 A. Let me just read this.

7 If I remember correctly, yes, there was
8 a discussion about what is the list of all
9 companies that do work in pain, and I think the
10 licensing people had started a list, and I then
11 proceeded to expand to all companies with an
12 interest in neuroscience and pain.

13 Q. Do you know whether Abbott followed up with any
14 of these companies to determine their interest
15 or potential interest in out-licensing 594?

16 A. I have the recollection that there may have been
17 contact with J&J.

18 Q. Where do you -- what do you recall in that
19 regard?

20 A. I'm not sure whether it was kind of something I
21 heard. I know at some point that there was a
22 discussion with J&J about partnership, but I
23 don't remember if that included 594. So I don't
24 know that my historical association between J&J
25 and 594 is -- you know, there is a basis for it,

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 and emesis.

2 Do you agree with that statement?

3 MR. PHILLIPS: Objection.

4 THE WITNESS: Yes, I would say most

5 significant dose-limiting side effect was nausea

6 and emesis. I can't speak to the parenthetical

7 comment of plasma levels greater than one ng per

8 ml.

9 (Marked for identification

10 Deposition Exhibit No. 63.)

11 BY MR. DAVIS:

12 Q. I'll show you, Dr. McCarthy, what's been marked

13 as Exhibit 63, and ask you to look at this

14 document and tell me, first, if you've seen it

15 before.

16 A. I don't remember this. This -- I don't remember

17 this, but this is consistent with work that I

18 was doing at -- in what I called before the

19 thread the needle effort and certainly looks

20 like slides that I have created in the past.

21 Q. If you would take a look, please, on the page --

22 it's page 14 of the slides. It's the one that

23 ends in 3298.UR. There is a reference there

24 again to the 114 study. Do you see that?

25 A. Yes.

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

1 Q. And under a section titled Tolerability &

2 Safety, the second sub-point says:

3 Significant discontinuation

4 rate of 66 percent due to AE at 300

5 micrograms BID.

6 A. Yes.

7 Q. Do you agree that the 114 study had a

8 significant discontinuation rate?

9 A. At the 300 microgram BID level.

10 Q. How about at any lower levels?

11 A. I don't know. I would have to revisit what

12 those were.

13 Q. What do you regard as a significant

14 discontinuation rate?

15 A. It depends on the context. It depends on the

16 disease. So in studies, long-term studies of

17 acute schizophrenia, there can be very commonly

18 rates of discontinuation greater than 50

19 percent, so --

20 Q. Was there an expected discontinuation rate for

21 the 114 study?

22 A. I don't think so.

23 Q. Was there a target discontinuation rate?

24 A. Not that I remember.

25 Q. If you'd take a look at the page 19 of the

McCarthy, M.D., Bruce Gerald (Linked) 09/29/2006 9:00:00 AM

- 1 slides, and the page that ends 3303.UR. Do you
- 2 see that?
- 3 A. 3303?
- 4 Q. Yes. It has to do with the design of the 114
- 5 study?
- 6 A. Yes.
- 7 Q. And under Power it says:
- 8 Planned: 80 percent for ES
- 9 0.46 with 80 slash group.
- 10 What does that mean?
- 11 A. 80 percent power for affect size .46 with 80 per
- 12 group.
- 13 Q. And then it says study. What does that mean?
- 14 A. I don't know.
- 15 Q. Is it the actual power of the study?
- 16 A. Yes, I think you are right.
- 17 Q. And it was less than what was planned; correct?
- 18 A. Yes.
- 19 MR. DAVIS: Why don't we take a break
- 20 for a couple of minutes.
- 21 (A brief recess was taken.)
- 22 BY MR. DAVIS:
- 23 Q. Dr. McCarthy, did you ever have any
- 24 responsibility with respect to ABT-518?
- 25 A. I can't remember.

SIGNATURE PAGE



BRUCE GERALD MCCARTHY, M.D.

10-NOV-2006

DATE

Subscribed and sworn to before me

this _____ day of _____, 2006.

Notary Public

County of _____ State of _____

My commission Expires: _____

McCarthy, Bruce Gerald (Linked) 3/16/2007 9:14:00 AM

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS

3

4

5 -----x

6 JOHN HANCOCK LIFE INSURANCE COMPANY

7 JOHN HANCOCK VARIABLE LIFE

8 INSURANCE COMPANY and MANULIFE

9 INSURANCE COMPANY (f/k/a INVESTORS

10 PARTNER INSURANCE COMPANY ,

11 Plaintiff,

12 Civil Action No.

13 V. 05-11150-DPW

14

15 ABBOTT LABORATORIES,

16 Defendant.

17 -----x

18

19

20

21 VIDEO DEPOSITION OF BRUCE GERALD MCCARTHY,

M.D., a witness called by counsel for the

22 Plaintiff, taken pursuant to the Federal Rules

of Civil Procedure, before Robert M. Miller,

23 Shorthand Reporter License No. 0010 and Notary

Public in and for the State of Connecticut, at

24 the Mystic Marriott, 625 North Road, Rte. 117,

Groton, CT on March 16, 2007, commencing at

25 9:14 a.m.

McCarthy, Bruce Gerald (Linked) 3/16/2007 9:14:00 AM

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17 By: Gregory D. Phillips, Esq.

18

19

20

21 VIDEOTAPED BY:

22 SEAN BUDD, ESQUIRE DEPOSITION SERVICES

23

24

25

1 DIRECT EXAMINATION BY MR. DAVIS:

2 Q. Good morning Dr. McCarthy. You understand that

3 we're continuing your deposition today?

4 A. Yes.

5 Q. And you need to respond verbally to the

6 questions?

7 A. Yes.

8 Q. And you need to answer truthfully, do you

9 understand that?

10 A. Yes.

11 Q. Did you prepare for your deposition today?

12 A. With Greg Phillips.

13 Q. Did you meet with Mr. Phillips in advance?

14 A. Yes.

15 Q. For how long?

16 A. Two hours.

17 Q. Did you review documents in the course of that

18 meeting?

19 A. Yes.

20 Q. Did you do anything else to prepare for your

21 deposition?

22 A. No.

23 Q. Have you reviewed the transcript from the

24 previous deposition?

25 A. At the time it was issued, I reviewed it and

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Would Abbott conduct a clinical trial of a
2 compound such as ABT-594 without having a
3 written protocol written beforehand?

4 A. No.

5 Q. When you worked at Abbott and you participated
6 in the development of ABT-594, were you aware
7 of all the clinical trials that were ongoing or
8 undertaken regarding that particular compound?

9 A. Yes.

10 Q. So was the 836 study something that would have
11 been under your supervision at some level?

12 A. I believe the 836 was under my supervision,
13 yes.

14 Q. There's a few other studies listed here.
15 There's a 984 study. What was that study?

16 A. I don't remember.

17 Q. There is an 833 study. What was that?

18 A. I believe 833 was the first neuropathic pain
19 study, but I'm not sure.

20 Q. Was the 836 study a phase one, phase two, or
21 phase three trial?

22 A. The 836 trial, I believe would have been a
23 phase two trial.

24

25 (At which time, Plaintiff's Exhibit

1 66 was marked for identification by the

2 Court Reporter.)

3

4 Q. Dr. McCarthy you have what's been marked as

5 Exhibit 66. Would you take a couple minutes to

6 look at this document and identify it for me,

7 if you can?

8 A. I've finished.

9 Q. Can you identify this for me?

10 A. It appears to an e-mail from myself.

11 Q. Do you recall sending this e-mail?

12 A. It seems generally familiar.

13 Q. The e-mail is dated October 29, 1999, correct?

14 A. Yes.

15 Q. Who were the people -- you don't have to

16 identify them by name, but the group of people

17 you sent the e-mail to, what does that

18 represent?

19 A. The group of Abbott employees.

20 Q. Were these people working on the ABT-594 team

21 in some way?

22 A. At this point I couldn't be sure of that or

23 not.

24 Q. The e-mail says, the first line: This e-mail

25 is being sent to introduce several changes in

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 the way the meetings for the ABT-594 project
2 are organized and introduces the ABT-594
3 Clinical Trials Team Meetings.

4 Do you see that?

5 A. Yes.

6 Q. Did you in fact have ABT-594 Clinical Trial
7 Team Meetings?

8 A. I don't remember.

9 Q. You don't recall attending a ABT-594 Clinical
10 Trial Team Meeting?

11 A. Not specifically.

12 Q. Do you recall setting up a variety of teams to
13 address the development of ABT-594?

14 A. Yes.

15 Q. It says further down on the first page under
16 ABT-594 Clinical Trials Team Meetings, it says:
17 The goal of the new monthly Clinical Trials
18 Team (CTT) Meetings.

19 Do you recall there were such meetings on
20 a monthly basis?

21 A. I don't remember.

22 Q. Do you recall seeing minutes of Clinical Trials
23 Team Meetings pertaining to 594?

24 A. I don't remember.

25 Q. The second page of this document, near the top

1 says: The status of clinical trials will be
2 communicated monthly by electronic distribution
3 of minutes to everyone involved with the
4 conduct and support of ABT-594 clinical trials.

5 Was that done?

6 A. I don't know.

7 Q. Do you have any reason to doubt that it wasn't
8 done?

9 A. Other than I don't remember, no.

10 Q. Do you recall rescinding the information or
11 instructions contained in this e-mail?

12 A. No.

13 Q. It says: In addition Gantt's will be updated.
14 What are Gantt's?

15 A. Charts that track the progress of a project.

16 Q. Were Gantt's charts prepared for ABT-594?

17 A. Yes.

18 Q. Were they prepared for the phase two trial or
19 the 114 trial?

20 A. Yes.

21 Q. How frequently were they updated?

22 A. I don't know.

23 Q. Who was responsible for maintaining the Gantt
24 charts for the 114 trial?

25 A. I don't remember.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Where were those charts kept?

2 A. I don't know.

3 Q. When you had your offices at Abbott back in the

4 2000-2001 timeframe, physically what building

5 were they located in?

6 A. I don't remember. I remember the visual

7 appearance of the building, but I don't

8 remember -- we were in two different bidding

9 and I don't remember their numbers at this

10 point.

11 Q. Was your office near Dr. Silber's office?

12 A. At one time it was. I don't remember during

13 that period whether it was or not.

14 Q. Was your office located near Mr. Biarnesen's

15 office?

16 A. Yes.

17 Q. Do you recall having Gantt charts pertaining to

18 the 114 trial located near your offices at

19 Abbott?

20 A. I don't remember.

21 Q. Do you recall having any charts pertaining to

22 the 114 trial located or outside near your

23 offices at Abbott?

24 A. Yes.

25 Q. You do? So you do have a recollection of that?

1 A. Yes.

2 Q. Who maintained those charts?

3 A. I don't know.

4 Q. What information was kept on the charts?

5 A. Information about the progress of the trial.

6 Q. What information, specifically?

7 A. Generally, start of study end of study,

8 database lock or projected database lock,

9 projected results. That would be general, I

10 don't remember specifically for these Gantt

11 charts.

12 Q. Was patient enrollment information tracked on

13 the Gantt charts?

14 A. I don't think so.

15 Q. How about adverse events?

16 A. No.

17 Q. What about premature terminations?

18 A. No.

19 Q. You said projected results. What projected

20 results were contained on the charts?

21 A. Projected date of results available.

22 Q. Any other projected information?

23 A. Not that I remember.

24 Q. Why did you keep the charts of that nature?

25 A. In order to forecast and track the progress of

1 A. I don't think so.

2 Q. Do you recall her keeping minutes in any way of
3 meetings pertaining to ABT-594?

4 A. No.

5 Q. Who was responsible for keeping minutes of 594
6 meetings?

7 MR. PHILLIPS: Objection to the
8 form.

9 A. It would depend on which meetings.

10 Q. Just above the ABT-594 Phase II-B Meetings is a
11 reference above to the ABT-594 Product
12 Development Team Meetings. Do you see that?

13 A. Yes.

14 Q. One of the outputs for that meeting listed on
15 page three are minutes. Do you see that?

16 A. Yes.

17 Q. It says minutes will be distributed to entire
18 ABT-594 Project Team. Do you see that?

19 A. Yes.

20 Q. Who was responsible for preparing the minutes
21 for those meetings?

22 A. I don't know who was responsible for the
23 minutes. It was different people at different
24 times.

25 Q. Did you receive copies of those minutes?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. I don't remember that I did, but you know, I
2 have no reason to doubt it.

3 Q. Was there someone at Abbott who was responsible
4 for maintaining a file of the minutes of the
5 meetings?

6 A. Not that I remember.

7 Q. When was the last time you had any
8 communications with Ms. Kacos?

9 A. Probably in November or December of last year.

10 Q. And what was the -- why did you have a
11 discussion with her at that point?

12 A. I believe she sent me an e-mail asking if it
13 was okay if Marlene Verlinden contacted me or
14 Kathy was looking to see if my e-mail at Pfizer
15 was still active or something along those
16 lines. She was in charge of facilitating a
17 contact between me and Marlene Verlinden.

18 Q. Ms. Kacos was still employed at Abbott at that
19 time?

20 A. Yes.

21 Q. This was 2006?

22 A. Yes. More specifically, the e-mail came from
23 the Abbott system so I infer that she was
24 employed, but I don't know.

25 Q. Did you speak with her at that time?

1 A. No.

2 Q. Ms. Kacos was still employed at Abbott when you
3 left Abbott, is that right?

4 A. Yes.

5 Q. Was she your administrative assistant up until
6 the time that you left Abbott?

7 A. No.

8 Q. She stopped being your administrative assistant
9 sometime prior to that?

10 A. Yes.

11 Q. Approximately when?

12 A. I don't remember when. Maybe in the last one
13 or two years before I left.

14 Q. Did you find Ms Kacos to be reasonably
15 competent?

16 A. Yes.

17 Q. Was she generally proficient?

18 A. Yes.

19 Q. Was she generally accurate in her work?

20 A. Generally accurate, yes.

21

22 (At which time, Plaintiff's Exhibit

23 67 was marked for identification by the Court

24 Reporter.)

25

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Dr. McCarthy you have what's been marked as
2 Exhibit 67 in front of you. Would you read
3 this document to yourself and tell me please
4 when you're done?

5 A. I'm finished.

6 Q. Do you recall receiving this e-mail in or about
7 January 2000?

8 A. I don't remember.

9 Q. Do you recall any of the discussions that are
10 referenced in the e-mail?

11 A. Only in general.

12 Q. The second paragraph, the first full paragraph
13 of this e-mail says -- it references a go/no-go
14 milestone for ABT-594. Is that right?

15 A. It does reference it, yes.

16 Q. It says there was a presentation on October 6,
17 1999. Do you see that?

18 A. Yes.

19 Q. Did you participate in that presentation?

20 A. I don't remember.

21 Q. Do you remember either of these studies, the
22 833 Neuropathic Pain or the 826 Osteoarthritis
23 Pain?

24 A. Yes.

25 Q. Do you recall presenting information or data

1 regarding those studies?

2 A. Yes.

3 Q. It says: Also presented were tolerability and

4 pharmacokinetic data from study M99-076 14 day

5 BID ascending fixed dose study.

6 Do you see that?

7 A. Yes.

8 Q. That was an ABT-594 study, correct?

9 A. Yes.

10 Q. It goes on to say: Based on the data it was

11 decided that ABT-594 will not proceed to Phase

12 3, but the program will continue with the

13 identification of maximum tolerated doses.

14 What was it about the data that was being

15 considered at that time that caused Abbott not

16 to proceed to Phase 3 with ABT-594?

17 A. I believe at the time we didn't have adequate

18 data to proceed to large pivotal studies that

19 would confirm the efficacy and safety of

20 ABT-594, that instead additional studies were

21 needed to understand the benefits and risks of

22 ABT-594 before proceeding to large pivotal

23 trials.

24 Q. Can you be more specific as to the data you

25 thought Abbott didn't have at that point in

1 time that would be necessary to move to Phase

2 3?

3 A. Only that this document refreshes my memory and

4 at least the items mentioned here about to what

5 extent titration could further help

6 tolerability, to what extent a different

7 formulation, the hard gelatin capsule could

8 help, and higher doses than were studied in 833

9 and 826.

10 Q. Did the tolerability results observed in these

11 studies play a role in the decision not the

12 proceed to Phase 3?

13 A. I don't remember.

14 Q. By tolerability -- the reference to

15 tolerability is a reference, among other

16 things, to nausea and vomiting, correct?

17 MR. PHILLIPS: Object to the form.

18 A. I don't know.

19 Q. You don't recall?

20 A. No.

21 Q. The second paragraph of this documents says,

22 among other things: Dosing has been completed

23 in study M99-120, which is an assessment of

24 whether titration improves the tolerability of

25 ABT-594 and/or allows higher doses to be

1 tolerated.

2 Do you see that?

3 A. Yes.

4 Q. Do you remember that study?

5 A. Only generally.

6 Q. It goes on to say: Although the data remain

7 blinded at this time, titration appears to

8 improve the tolerability of ABT-594.

9 Do you see that?

10 A. Yes.

11 Q. How was it that Abbott was determining that

12 titration appeared to improve the tolerability

13 of ABT-594 if the study was still blinded?

14 MR. PHILLIPS: Object to the form.

15 A. I think in this study, which was a small study

16 in which very high levels of the drug were

17 being used, it wasn't, functionally, not a

18 blinded study because the doses were so high

19 that all subjects that were receiving 594 had

20 adverse events. So one could infer how those

21 adverse events -- one could already know which

22 patients were receiving drug and which were

23 receiving placebo.

24 Q. It says here the data remained blinded. Are

25 you saying the data was not blinded?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. The data, in a formal way, were blinded. But
2 in a operationally the data was unblinded
3 because the casual observer could tell all the
4 patients were at a single site, all data were
5 available by patient, even though it was
6 blinded, and one knew immediately which
7 patients were receiving drug and which were not
8 at these high doses.

9 Q. So it was possible to divine some information
10 about the trial even though the data was
11 blinded?

12 A. That's correct.

13

14 (At which time, Plaintiff's Exhibit
15 68 was marked for identification by the
16 Court Reporter.)

17

18 Q. Dr. McCarthy, you have what's been marked as
19 Exhibit 68. Would you look at the document and
20 tell me if you've ever seen it before?

21 A. It looks generally familiar as the protocol
22 M99-114.

23 Q. Is that your signature in the first page of
24 this document?

25 A. Yes, it is.

1 Q. If you turn please to the page of this document

2 that the bates number ends in 5838?

3 A. Okay.

4 Q. You see there is a reference to session 8.20

5 study objectives?

6 A. Yes.

7 Q. Would you read that section and tell me when

8 you're done?

9 A. Just the paragraph or the section?

10 Q. Just the paragraph.

11 A. I'm finished.

12 Q. Did the 114 study meet these objectives?

13 A. I believe it did, yes.

14 Q. Did it meet them to the statistical power that

15 Abbott originally anticipated or designed?

16 A. I don't know.

17 Q. Who would know that?

18 A. I don't know who in particular -- a

19 statistician would be able to answer that.

20 Q. Mr. Thomas for example?

21 MR. PHILLIPS: Object to the form.

22 A. I don't remember. I've forgotten whether he

23 was the statistician but he would have the

24 capabilities to do so.

25 Q. You don't recall Mr. Thomas working on the 114

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 criteria relating to that laboratory test, and

2 excluding additional medications.

3 Q. Would you look at the page bates number ending

4 5903?

5 A. Yes.

6 Q. Is that your signature on this page?

7 A. Yes, it is.

8 Q. And by putting your signature on this page were

9 you approving this protocol as amended?

10 A. Yes.

11 Q. Who drafted this protocol?

12 A. I don't remember. Based on the signatures here

13 it would have been Fred Siebert, but I don't

14 have a personal memory that he was or was not

15 the person.

16 Q. Did you play a role in the creation of this

17 protocol?

18 A. Of the protocol?

19 Q. Yes?

20 A. Of the protocol, yes.

21 Q. What role did you have?

22 A. As I guess the person who primarily designed

23 the protocol.

24 Q. What does it mean to design the protocol?

25 A. To put together the general elements of the end

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 points that would be used, inclusion and

2 exclusion criteria, medications to be allowed

3 or disallowed, safety assessments.

4 Q. Who determined the -- how Abbott would go

5 about -- strike that.

6 Did you play any role in determining what

7 the statistical power or anticipated

8 statistical power of the study would be?

9 A. Not specifically.

10 Q. Generally?

11 A. In a general way I would participate in

12 conversations but the statisticians would be

13 the primary determiners of the statistical

14 power.

15 Q. So the person or people at Abbott who would be

16 responsible for determining the appropriate

17 statistic power for the study would be

18 Mr. Morris or Mr. Thomas?

19 A. Yes.

20 Q. You would adopt their recommendations in that

21 respect?

22 A. Yes.

23

24 (At which time, Plaintiff's Exhibit

25 70 was marked for identification by the

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. To you recall at any point in time funding for

2 ABT-594 in 2001 being reduced?

3 A. I'm forgetting my years, so I don't remember.

4 Q. Do you know who Howard is, as referenced here?

5 A. No, I don't.

6 Q. Who within Abbott made decisions on whether to
7 fund particular clinical studies?

8 MR. PHILLIPS: Objection to form.

9 A. It would have been head of development at the
10 time. I assume that was John Leonard. I can't
11 remember though.

12

13 (At which time, Plaintiff's Exhibit

14 71 was marked for identification by the

15 Court Reporter.)

16

17 Q. Dr. McCarthy, would you look at what's been

18 marked as Exhibit 71 at your deposition? Read

19 this document to yourself and tell me please

20 when you're done.

21 A. I'm done.

22 Q. Have you seen this document before?

23 A. I don't remember it.

24 Q. Do you know the author of this e-mail?

25 A. The name seems familiar, but I don't remember.

1 the 114 was underway about the possibility of
2 removing the high dose group?

3 A. I don't remember.

4 Q. You have no recollection of that?

5 A. No.

6 Q. Do you recall discussions within Abbott about
7 making any changes to the 114 study while that
8 study was underway?

9 A. Yes.

10 Q. What do you recall?

11 A. At various times we talked about changing the
12 study inclusion/exclusion criteria to help with
13 enrollment or to modify based on safety issues
14 to ensure that the patients coming into the
15 study were the right people, to discuss whether
16 or not fewer or more patients should be
17 enrolled in the study. Those are the specific
18 items that come to mind.

19 Q. Do you recall ever proposing to make any
20 changes in the protocol based on what you
21 perceived to be tolerability issues that were
22 cropping up in the course of the trial?

23 A. Generally, yes.

24 Q. What do you recall?

25 A. I don't, just that there were discussions about

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 in what ways we could improve recruitment for
2 the study by changing the types of patients who
3 come in.

4 Q. Anything more?

5 A. No

6

7 (At which time, Plaintiff's Exhibit

8 72 was marked for identification by the

9 Court Reporter.)

10

11 Q. Dr. McCarthy would you take a moment please to

12 read Exhibit 72 to yourself and tell me when

13 you're done?

14 A. I'm done.

15 Q. Do you recall sending this e-mail?

16 A. Not specifically.

17 Q. Generally?

18 A. Yes.

19 Q. This is an e-mail to Mr. Morris and to Jim

20 Thomas. They both did statistical work at

21 Abbott?

22 A. That's correct.

23 Q. And Ms. Landsberg, she was on the commercial

24 side?

25 A. Yes.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. And Mr. Biarnesen, he was the operations

2 manager for the 594, correct?

3 A. Yes.

4 Q. Ms. Collicott was in charge of operations for

5 the 114 study, correct?

6 A. That's correct.

7 Q. Why did you choose these particular people to

8 send this e-mail to?

9 A. I don't know.

10 Q. The subject of e-mail is protocol change

11 discussion. Do you see that?

12 A. Yes.

13 Q. Do you recall that discussion?

14 A. No.

15 Q. The first line says: I've scheduled a meeting

16 next week to discuss options to modify the 114

17 protocol. Enrollment has not met initial

18 expectations.

19 Do you see that?

20 A. Yes.

21 Q. Now this is back in July of 2000?

22 A. Correct.

23 Q. And at that point you were concerned about

24 enrollment for the 114 trial, correct?

25 MR. PHILLIPS: Objection to the

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 form.

2 A. I don't remember particularly, but this

3 certainly seems to suggest it.

4 Q. Now the second paragraph says: Of the 78

5 subjects enrolled to date, at least 31 have

6 preterm.

7 Meaning they had prematurely terminated,

8 correct?

9 A. I assume that's what it means.

10 Q. It says: Of those, at least 20 appear to have

11 preterm for AE's typical of our drug (nausea,

12 vomiting, and/or dizziness).

13 AE is a reference to adverse events,

14 correct?

15 A. Correct.

16 Q. Although three of these subjects dropped on day

17 one (when they would have, at most, been

18 exposed to 75 micrograms) many of these

19 subjects dropped in the 3-11 day time frame

20 (the period of dose escalation resulting in 150

21 micrograms BID at day 4, 225 micrograms BID at

22 day 6, and 300 micrograms BID at day 8.

23 Do you see that?

24 A. Yes.

25 Q. And it's fair to say, Dr. McCarthy, at this

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 point in time what you were trying to do was
2 make some preliminary or some educated guesses
3 about what it was that was causing participants
4 in the trial to preterm, correct?

5 MR. PHILLIPS: Object to the form.

6 A. I don't remember what I was thinking at the
7 time.

8 Q. Looking at the e-mail, does it cause you to
9 conclude that what you were doing at that point
10 in time was trying to make a best estimate as
11 to what it was that was causing patients to
12 drop out of the trial prematurely?

13 MR. PHILLIPS: Object to the form.

14 A. Yes.

15 Q. Pardon me?

16 A. Yes.

17 Q. And you were doing that based on the blinded
18 data, correct?

19 A. Yes.

20 Q. So just looking at the blinded data you had
21 some indication that patients were dropping out
22 in part because they were receiving escalating
23 doses of ABT-594. Is that fair to say?

24 MR. PHILLIPS: Object to the form.

25 A. I would say I didn't know.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Not saying you didn't know, but you had some
2 inkling that was probably the case, is that
3 right?

4 MR. PHILLIPS: Object to the form.

5 A. I would say no. I had a hypothesis.

6 Q. And educated hypothesis?

7 MR. PHILLIPS: Object to the form.

8 A. I would say a hypothesis.

9 Q. But enough of a hypothesis that you were
10 proposing perhaps making some changes to the
11 protocol on the basis of that hypothesis,
12 correct?

13 A. Yes.

14 Q. Is it fair to say at this point in time you had
15 a belief that more likely than not the
16 premature terminations that were being observed
17 in the study were due to escalated doses of
18 ABT-594?

19 A. I don't know, I don't think so.

20 Q. What was it about the 300 microgram dose that
21 caused you to believe that it might be in
22 Abbott's best interests to drop that dose from
23 the study?

24 MR. PHILLIPS: Object to the form.

25 A. I don't really remember.

1 Q. Did you think that more likely than not that
2 the 300 microgram dose was causing patients to
3 experience nausea and vomiting?

4 MR. PHILLIPS: Same objection.

5 A. More likely than not.

6 Q. Again, that's all information you garnered, at
7 least preliminarily, from the blinded data, is
8 it not?

9 MR. PHILLIPS: Object to the form.

10 A. I don't remember.

11 Q. Did you have any unblinded data at this point
12 in time in July of 2000?

13 A. No.

14 Q. So the hypothesis that you were forming at that
15 point in time could only have been based on
16 blinded data, is that correct?

17 A. That's correct.

18 Q. Do you recall any discussions within Abbott
19 around this proposed protocol change?

20 A. No.

21 Q. Nothing?

22 A. No.

23 Q. Do you recall anything that Dr. Silber had to
24 say at that point?

25 A. No.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 today?

2 A. No.

3

4 (At which time, Plaintiff's Exhibit

5 75 was marked for identification by the Court

6 Reporter.

7

8 Q. Dr. McCarthy, you have Exhibit 75 in front of

9 you. Would you take a moment and read this

10 document and tell me when you're done reading

11 it?

12 A. I'm done.

13 Q. This appears to be an email from Ms. Landsberg

14 to you, among others at Abbott dated October 3,

15 2000. Do you see that?

16 A. Yes.

17 Q. Do you have any reason to believe you did not

18 receive this email?

19 A. No, other than I don't remember it.

20 Q. The email references ABT 594/963 Purdue

21 meeting. Do you see that?

22 A. Yes.

23 Q. What was 963?

24 A. ABT-963 was a COX-2 inhibitor.

25 Q. And what was the Purdue meeting?

1 A. I don't remember.

2 Q. The email itself says: Bob, as you, Rose and I

3 had discussed, if we move forward to set up a

4 presentation of information to Purdue, the

5 following people could probably do the

6 presenting on key topics.

7 Do you see that?

8 A. Yes.

9 Q. And your name is listed next to Clinical ABT

10 594?

11 A. Yes.

12 Q. Do you recall making any presentations at any

13 point in time to any representatives of Purdue

14 Pharma concerning ABT-594?

15 A. No.

16 Q. Do you recall ever having any discussions with

17 anyone at Abbott concerning a potential

18 partnering or co-development relationship with

19 anyone at Purdue concerning ABT-594?

20 A. No.

21 Q. You have no recollection of that whatsoever?

22 A. No.

23 Q. Do you have any recollection of ever having any

24 discussions with anyone at Abbott about

25 partnering or entering a co-development

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 relationship with any other company concerning

2 ABT-594?

3 A. Not about any other companies.

4 Q. What do you recall?

5 A. That at some point, I don't remember when,

6 others introduced the idea of partnering with

7 other companies.

8 Q. When you say partnering with other companies,

9 is this with respect to ABT-594?

10 A. Yes.

11 Q. Who do you recall raising that issue?

12 A. I don't remember.

13 Q. You have no recollection of who it was within

14 the Abbott organization that raised that issue?

15 A. No.

16 Q. What do you recall about that?

17 A. Only that -- only a general sense that

18 discussions -- that I was involved in

19 discussions that people raised the possibility

20 of partnering and we talked about the risks of

21 disclosing where we were on this drug and the N

22 & R franchise.

23 Q. Do you recall the names of any entities with

24 whom partnering was considered?

25 A. No.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. About halfway through the e-mail in the
2 paragraph that states: The study currently has
3 79 subjects randomized to the original four arm
4 protocol. There is some concern with what may
5 be AE's due to the higher 300 microgram dose
6 and also other study design elements.

7 Do you recall discussions within Abbott
8 about concern associated with any concerns
9 about adverse events potentially associated
10 with the 300 microgram dose?

11 A. No.

12 Q. This doesn't refresh your recollection in any
13 way on that topic?

14 A. No.

15

16 (At which time, Plaintiff's Exhibit
17 77 was marked for identification by the
18 Court Reporter.)

19

20 Q. Dr. McCarthy, you have what's been marked as
21 Exhibit 77. Would you look at the -- look at
22 the document and identify it if you can?

23 A. It states that it's the minutes in the ABT-594
24 product development meeting.

25 Q. Do you recall seeing minutes like this when you

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 were working on the ABT-594 team?

2 A. No.

3 Q. Do you recall receiving minutes?

4 A. Yes.

5 Q. But they didn't take this form?

6 A. I don't remember.

7 Q. Do you have any reason to doubt these are not

8 minutes of that ABT-594 Product Development

9 Team Meeting?

10 MR. PHILLIPS: Object to the form.

11 A. Other than I don't remember, no.

12 Q. It lists attendees at this meeting to include

13 you and Dr. Silber, do you see that?

14 A. Yes.

15 Q. Do you have any recollection of this particular

16 meeting?

17 A. No.

18 Q. One of the last people listed is Kathy Kacos,

19 do you see that?

20 A. Yes.

21 Q. If you look in the lower left hand corner, do

22 you see the reference to 8/21/00?

23 A. Yes.

24 Q. And it says CKK and it looks like an M, and

25 then it says product development team/minutes

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 080100. Do you see that?

2 A. Yes.

3 Q. Are those Ms. Kacos' initials as best as you

4 can tell?

5 MR. PHILLIPS: Object to the form.

6 A. They may be.

7 Q. Does this refresh your recollection as to

8 whether Ms. Kacos prepared minutes of product

9 development team meetings?

10 A. No.

11 Q. But she did attend them?

12 A. I don't remember.

13 Q. These minutes indicate that the Product

14 Development Team met on Tuesday, August 1,

15 2005 in AP30-3E-Cafeteria. Do you see that?

16 A. Yes.

17 Q. There's got to be an easier nomenclature

18 system. Do you recall meeting in that

19 location?

20 MR. PHILLIPS: Object to form.

21 Q. Do you recall having Product Development Team

22 Meetings in that location?

23 A. No.

24 Q. Would you turn please to the last page of

25 Exhibit 77. Have you seen this document

1 before?

2 A. Not that I remember, no.

3 Q. If you look at the last page of -- would you

4 read the first paragraph and tell me when

5 you're done?

6 A. I'm done.

7 Q. It says that, among other things: Currently we

8 have 99 subjects randomized -- let me go back.

9 Marilyn Collicott provided an update on

10 the M99-194 neuropathic pain study. Do you see

11 that?

12 A. Yes.

13 Q. Do you recall Ms. Collicott providing updates

14 on that study during the course of the study?

15 A. Yes.

16 Q. It goes on to say: Currently we have 99

17 subjects randomized with an approximate 50%

18 screen failure rate. Our goal of enrollment is

19 320 subjects. There has been much concern with

20 the dropout rate.

21 Why was there much concern with the

22 dropout rate at that point in time?

23 MR. PHILLIPS: Objection to the

24 form.

25 A. I don't remember why at the time.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. It goes on to say: Therefore, we have sent out
2 surveys to each site to determine who and why
3 subjects are dropping out.

4 Do you see that?

5 A. Yes.

6 Q. What surveys are being referred to there?

7 A. I don't know.

8 Q. Who authorized the survey of investigator sites
9 for the 114 trial?

10 MR. PHILLIPS: Objection to the
11 form.

12 A. I don't remember.

13 Q. Do you recall such a survey being done?

14 A. Yes.

15 Q. Who took the survey?

16 A. I don't remember.

17 Q. What form did the survey take?

18 A. I don't know.

19 Q. Was it a written survey?

20 A. I don't know.

21 Q. Did it involve talking to investigators?

22 A. Probably.

23 Q. Did you participate in the survey in any way?

24 A. I don't know. I don't remember.

25 Q. Did you ever see any results from the survey?

1 A. I don't remember.

2 Q. Specifically what did the survey ask?

3 A. I don't remember.

4 Q. You have no recollection of what the survey

5 asked?

6 A. No.

7 Q. Do you have any recollection of who at Abbott

8 participated in actually undertaking the

9 survey?

10 A. Possibly Marilyn Collicott.

11 Q. Anyone else?

12 A. No.

13 Q. What was the purpose of the survey?

14 MR. PHILLIPS: Object to the form.

15 A. The survey that is mentioned here in terms of

16 determining who and why subjects are dropping

17 out -- the survey that I remember was to find

18 out what factors investigators could identify

19 that was limiting finding patients and

20 recruiting patients, and also as to why

21 patients may or may not be staying in the

22 study.

23 Q. Was one of the purposes of the study to find

24 out whether patients were dropping out due to

25 nausea and vomiting?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. I don't know.

2 Q. Was the survey completed?

3 A. I don't know.

4 Q. Do you know whether anyone at Abbott ever

5 reviewed any results of that survey?

6 A. I don't remember.

7 Q. Did you ever receive any report regarding the

8 survey?

9 A. I don't think so.

10 Q. Do you recall following up with anyone at

11 Abbott to find out what the results of the

12 survey were?

13 A. I don't remember.

14 Q. Do you recall having any discussions with

15 Ms. Collicott regarding the survey?

16 A. No.

17 Q. How about Dr. Silber?

18 A. No.

19

20 (At which time, Plaintiff's Exhibit

21 78 was marked for identification by the

22 Court Reporter.)

23

24 Q. Dr. McCarthy, you have what's been marked as

25 Exhibit 78 that is another set of product 594

1 A. I don't remember.

2 Q. Do you recall Mr. Thomas sending you

3 information concerning adverse event rates for

4 different arms of the 114 study at any point in

5 time?

6 A. Yes.

7 Q. Why were you interested in that information?

8 A. The information I remember him sending at any

9 time included the results of the study.

10 Q. Do you recall, before the data being unblinded,

11 Mr. Thomas sending any of that information?

12 A. I don't remember.

13 Q. Do you recall why it was that Mr. Thomas was

14 sending you this information back in August of

15 2000?

16 A. No.

17 Q. Do you recall being interested in the drop out

18 rates pertaining to nausea, vomiting, and

19 dizziness back in August of 2000?

20 A. No.

21 Q. Do you recall any discussions with Mr. Thomas

22 on that topic before the data was unblinded?

23 A. No.

24 Q. How about Mr. Morris?

25 A. No.

1 Do you see that?

2 A. Yes.

3 Q. What recent study are you referring to there?

4 A. I don't remember.

5 Q. At this point in time you had some survey, is

6 that right?

7 A. I believe that's true.

8 Q. As you sit here today you have no recollection

9 of the survey you're referring to?

10 A. I don't.

11 Q. Do you recall whether that's a reference to a

12 recent survey in Exhibit 81 or is a reference

13 to the survey that we saw referenced in the --

14 mentioned in the development team meeting

15 minutes marked Exhibits 77 and 78?

16 A. I don't know if it's the same survey.

17 Q. When you made your investigative site visits,

18 did you learn any more about when patients were

19 experiencing adverse events of nausea vomiting

20 and dizziness in the course of the trial?

21 A. I don't remember

22

23 (At which time, Plaintiff's Exhibit

24 82 was marked for identification by the

25 Court Reporter.)

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

- 1 [REDACTED]
- 2 Q. Dr. McCarthy you have Exhibit 82 in front of
- 3 you. Would you read this document to yourself
- 4 and tell me when you're done?
- 5 A. I'm done.
- 6 Q. Who is Mike Williams?
- 7 A. Mike Williams was Head of Neuroscience
- 8 Discovery at Abbott.
- 9 Q. Was he above you in the hierarchy?
- 10 A. He was in a different hierarchy, but he was
- 11 Vice President, so in general, yes.
- 12 Q. Did you work with Mr. Williams in any way with
- 13 respect to the development of ABT-594?
- 14 A. Yes.
- 15 Q. What was Mr. Williams' role in this regard?
- 16 A. He led the discovery organization team that
- 17 included the teams that discovered ABT-594 and
- 18 the NNR's.
- 19 Q. Did Mr. Mike Myer work for Mr. Williams?
- 20 A. He worked in his organization.
- 21 Q. This e-mail is directed to the Jennifer Smoter
- 22 with a CC to Dr. Silber, do you see that?
- 23 A. Yes.
- 24 Q. Who was Jennifer Smoter?
- 25 A. I believe she was in public affairs.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. There's also reference to Mike Decker. Who was
2 Mike Decker?

3 A. Mike was another basic scientist in Mike
4 Williams' organization.

5 Q. The e-mail says: Jennifer, I think Mike Decker
6 has addressed some of document issues. Another
7 real issue we must address given some of
8 internal discussions around the clinical trials
9 on ABT-594 is whether we want to make any
10 statements in the next few weeks until a
11 decision is made by Jeff Leiden as to whether
12 we continue the trials.

13 Do you see that?

14 A. Yes.

15 Q. Do you recall internal discussions around the
16 clinical trials of ABT-594 in the October 2000
17 time frame?

18 A. No.

19 Q. Do you recall whether Abbott was considering
20 making any statements regarding ABT-594 in and
21 around the October 2000 time frame?

22 A. No.

23 Q. Do you recall at any point in time whether
24 there was a question whether Mr. Leiden was
25 going to stop clinical trials of ABT-594?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. No.

2 Q. You never heard that at that point?

3 A. No.

4 Q. Do you recall whether there was a decision that

5 was being teed up for Mr. Leiden in the fall or

6 early winter of 2000 regarding whether clinical

7 trials for ABT-594 would continue?

8 MR. PHILLIPS: Object to the form.

9 A. I don't remember.

10 Q. Do you recall any discussions at all with Dr.

11 Leiden in the fall or winter of 2000 concerning

12 whether clinical trials of ABT-594 would

13 continue?

14 A. No.

15 Q. Do you recall having discussions with anyone at

16 Abbott in the fall of 2000 or the winter of

17 2000-2001 concerning whether Abbott would

18 continue clinical trials of ABT-594?

19 A. No.

20

21 (At which time, Plaintiff's Exhibit

22 83 was marked for identification by the

23 Court Reporter.)

24

25 Q. Dr. McCarthy you have in front of you Exhibit

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Who is Larry Lin, L-I-N?

2 A. I don't remember.

3 Q. Do you recall interacting with Mr. Lin in any
4 way concerning a potential partnering or
5 co-development relationship involving ABT-594?

6 A. No.

7

8 (At which time, Plaintiff's Exhibit
9 84 was marked for identification by the
10 Court Reporter.)

11

12 Q. Dr. McCarthy you have in front of you what's
13 been marked as Exhibit 84. Would you read this
14 document to yourself and tell me when you are
15 done?

16 A. I'm done.

17 Q. This appears to be a couple of e-mails, one
18 from Mr. Weiland and one from Mr. Sullivan and
19 they were sent to you at Abbott. Do you see
20 that?

21 A. Yes.

22 Q. Do you recall receiving these e-mails?

23 A. No.

24 Q. Do you have any reason to doubt that you
25 received them?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. Other than I don't remember, no.

2 Q. I think the first email in time is the one at

3 the bottom of page one of Exhibit 84 and

4 continues on page two, do you see that?

5 A. Yes.

6 Q. That one is dated November 1, 200 and addressed

7 directly to you from Mr. Weiland, do you see

8 that?

9 A. Yes.

10 Q. It says: Bruce thank you for your message.

11 Unfortunately with everyone's travel calendar,

12 a pre-planning meeting has not been very

13 feasible.

14 Do you see that?

15 A. Yes.

16 Q. And the subject is re: Pharmacia meeting?

17 A. Yes.

18 Q. Do you recall trying to set up a pre-planning

19 meeting concerning a meeting with Pharmacia?

20 A. I don't remember.

21 Q. Mr. Weiland's email to you goes on to state:

22 The primary purpose for this meeting is to

23 share data with Pharmacia that might encourage

24 them to partner with us on this project.

25 Do you see that?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. Yes.

2 Q. Do you understand this project to be ABT-594?

3 A. I don't remember.

4 Q. The e-mail goes onto state: At the end of the

5 day there is no other way I am aware of to

6 broach a partnership without disclosure of the

7 technical and scientific information. Hence,

8 unless there is something particular that we

9 should hold back in this first round, we need

10 to provide the info. One area where I have a

11 concern is the nausea and vomiting issue. If

12 anyone has a suggestion on how we can handle

13 that without frightening our partner it would

14 be very well received.

15 Do you see that?

16 A. Yes.

17 Q. What do you recall about discussions within

18 Abbott about the potential for nausea and

19 vomiting issue to potentially frighten a

20 partner on co-development of ABT-594?

21 A. I don't recall.

22 Q. You don't recall why it was that Mr. Weiland

23 thought the information about nausea and

24 vomiting might frighten away a potential

25 partner on ABT-594?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 MR. PHILLIPS: Objection to the

2 form.

3 A. I don't know.

4 Q. The top e-mail is an e-mail from James Sullivan

5 back to Mr. Weiland and also to you. Do you

6 see that?

7 A. Yes.

8 Q. He mentions the possibility -- he says: I

9 would suggest the agenda etc. should be limited

10 to including a preclinical profile of ABT-594

11 and a bulk of time.

12 Do you see that?

13 A. Yes.

14 Q. Did you participate in assembling any

15 information concerning clinical data involving

16 ABT-594 for presentation to any other

17 companies?

18 A. I don't remember.

19 Q. As you sit here today you have no recollection

20 of participating in such presentations, is that

21 right?

22 A. That's correct.

23 Q. Back in the November 2000 time frame did you

24 think that the nausea and vomiting that had

25 been observed in clinical trials of ABT-594 was

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 enough to perhaps cause a potential

2 co-development partner to shy away or refuse to

3 engage in a co-development relationship?

4 A. No.

5 Q. So you thought Mr. Weiland's comments about the

6 possibility of that information frightening a

7 partner was unjustified?

8 A. Yes.

9 Q. What do you recall from discussions on that

10 topic at that time?

11 A. I don't recall any discussions.

12 Q. This doesn't refresh your recollection in any

13 way about discussions with potential

14 co-development partners?

15 A. No.

16

17 (At which time, Plaintiff's Exhibit

18 85 was marked for identification by the

19 Court Reporter.)

20

21 Q. Dr. McCarthy would you look at Exhibit 85.

22 Please read it to yourself and tell me when

23 you're done?

24 A. I'm done.

25 Q. It appears to be an e-mail from you Dr.

1 A. Yes.

2 Q. And it's in green. Do you see that?

3 A. Yes.

4 Q. And if you look at the key in the right hand

5 corner it's listed and it says green means

6 questionable viability. Do you see that?

7 A. Yes.

8 Q. Do you recall learning about December of 2000

9 that Dr. Leiden was making presentations that

10 identified ABT-594 as having questionable

11 viability?

12 A. No.

13 Q. You don't deny you got a copy of this

14 presentation back in December of 2000?

15 A. Other than I don't remember receiving it.

16 Q. Would it have been significant to you in that

17 time frame to learn that Dr. Leiden -- who I

18 think was the head of pharmaceutical business

19 at Abbott, correct?

20 A. I don't remember if that was his role at the

21 time, but it could have been.

22 Q. I'm sorry. He was the Chief Scientific

23 Officer, correct?

24 A. That may have been.

25 Q. Would it have been significant to you to learn

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 that the Chief Scientific Officer for Abbott
2 back in December 2000 was identifying ABT-594
3 as having questionable viability?

4 A. No.

5 Q. That wouldn't have meant anything to you?

6 A. No.

7 Q. We see other compounds here listed as uncertain
8 viability?

9 A. Yes.

10 Q. And you understand questionable viability to be
11 worse than uncertain viability?

12 MR. PHILLIPS: Objection. Assumes
13 facts not in the record -- object to the form.

14 A. I don't know what these terms mean.

15 Q. Do you recall any discussion in and around
16 December 2000 concerning Dr. Leiden's
17 presentation?

18 A. .

19 Q. Nothing?

20 A. No.

21 Q. No water cooler discussion, nothing along those
22 lines when he listed ABT-594, one of the
23 compounds you were working on, as having
24 questionable viability?

25 MR. PHILLIPS: Object to the form.

1 A. No.

2 Q. Do you have any idea as why it was that Dr.

3 Leiden regarding ABT-594 said it had

4 questionable viability back in late 2000?

5 MR. PHILLIPS: Object to the form.

6 A. No

7

8 (At which time, Plaintiff's Exhibit

9 91 was marked for identification by the

10 Court Reporter.)

11

12 Q. Dr. McCarthy would you look at Exhibit 92 for a

13 moment and read it to yourself and tell me

14 please when you are done?

15 A. I'm done.

16 Q. Have you seen this document before?

17 A. In preparation with Mr. Phillips.

18 Q. The very last page of Exhibit 91 is an email

19 from you to Mr. Thomas dated December 20, 2000.

20 Do you see that?

21 A. Yes.

22 Q. It is references n/v rate and that is a

23 reference nausea and vomiting rate?

24 A. I believe that's correct.

25 Q. And that's a nausea and vomiting rate for the

1 114 study, correct?

2 A. I assume.

3 Q. What was it that you were looking for from

4 Mr. Thomas at that point in time?

5 A. I don't know.

6 Q. Why were you asking Mr. Thomas for information

7 about the nausea and vomiting rate in the 114

8 study at that point in time?

9 A. I don't remember.

10 Q. The first page of Exhibit 91 is an e-mail from

11 you to Mr. Thomas that says: Thanks, I assume

12 to get the AE rates for the entire blinded

13 population I add up the N's in the columns.

14 Thus, the total N in the database below is 129

15 and there are a total of 25 nausea's (19%) and

16 10 vomitings (7.8%), and 9 ladies dancing.

17 A. It does say that, yes.

18 Q. What is the reference to N?

19 A. Capital N generally refers to a sample number

20 so that's what I would infer.

21 Q. Why was it you were interested in calculating

22 the N's for this particular study at this point

23 in time?

24 A. I don't remember.

25 Q. Who is Rich Manski?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 you asked him about accessing that database?

2 A. I don't remember. I think at one point I asked

3 him about it and the system wasn't set up yet.

4 I can't remember. Only vague memories of this.

5 Q. Do you know, if anything, what you did with the

6 data you obtained from Mr. Thomas?

7 A. No.

8 Q. As you sit here today you don't have any

9 recollection as to why you were interested in

10 nausea and vomiting rates in the study of 114

11 in December of 2000?

12 A. No.

13 Q. Was that a particular area of concern for you

14 at that time?

15 A. I don't remember if it was at that time.

16 Q. Was it a particular area of concern for you at

17 any point in time before the data was

18 unblinded?

19 A. Yes.

20 Q. When did it first become a concern for you?

21 A. I think within days of joining Abbott in the

22 first study in which nausea and vomiting was

23 first observed in the first trial of ABT-594.

24 Q. Is there anything about the preliminary

25 results, the blinded data of the 114 trial that

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 caused you to have concern about nausea and
2 vomiting?

3 A. Not incrementally, no.

4

5 (At which time, Plaintiff's Exhibit
6 92 was marked for identification by the
7 Court Reporter.)

8

9 Q. Dr McCarthy would you read this document to
10 yourself please and tell me when you're done?

11 A. I'm done.

12 Q. Have you seen this document before?

13 A. Yes in preparation with Mr. Phillips.

14 Q. It appears to be two e-mails, one from you to
15 Ms. Andrea Landsberg on December 21, 2000 and
16 another one forwarding a copy of your e-mail to
17 Dr. Silber. Do you see that?

18 A. Yes.

19 Q. Did you actually send these e-mails?

20 A. I only vaguely remember.

21 Q. Do you have any reason to doubt you sent these
22 e-mails?

23 A. Other than I only vaguely remember.

24 Q. The first one in time from you to

25 Ms. Landsberg -- actually let me start at the

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 top, your e-mail to Dr. Silber says: Andrea as
2 part of the portfolio process from the other
3 day, asked that I give her an update on the
4 nausea and vomiting story.

5 What is the portfolio process that you
6 refer to?

7 A. I don't know.

8 Q. Then it references she asked for an update on
9 the nausea and vomiting story?

10 A. I can only assume the question of nausea and
11 vomiting.

12 Q. When you say the question of nausea and
13 vomiting you mean the incidence of nausea and
14 vomiting in clinical trials of ABT-594?

15 A. Yes.

16 Q. Including the 114 trial?

17 A. Yes.

18 Q. It says you told Dr. Silber: Yesterday I sent
19 her the 833/826 rates. Here's what I sent her
20 on 114.

21 And that's a reference to information on
22 the 114 trial?

23 A. I assume, yes.

24 Q. And as of December 2000 all the data on the 114
25 trial was still blinded, correct?

1 A. Correct.

2 Q. So what you were sending Ms. Landsberg was

3 information based on your review of the blinded

4 data, correct?

5 A. Yes.

6 Q. And the information you sent to her said:

7 Remember this is blinded, that means the rates

8 include data for all groups combined (so,

9 probably very low nausea and vomiting in

10 placebo and higher rates in the 300 mcg BID

11 group).

12 Did I read that correctly?

13 A. Yes.

14 Q. If I understand what you're saying there

15 correctly, you're saying the data was blinded

16 but based on what you could tell at that point

17 in time the data was probably such that there

18 were very low nausea and vomiting among

19 subjects who took placebo, but the rates of

20 nausea and vomiting increased and you had

21 higher rates of nausea and vomiting among

22 people who were taking 300 micrograms. Is that

23 right?

24 MR. PHILLIPS: Object to the form.

25 A. That would be the hypothesis, yes.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. That's the information you provided to Ms.

2 Landsberg at that point in time, correct?

3 A. It appears so, yes.

4 Q. And it says probably, so that would be what you

5 believe more likely than not in December 2000.

6 Is that correct?

7 A. Yes.

8 Q. At this point in time you sent this e-mail to

9 Ms. Landsberg did you think the nausea and

10 vomiting story -- strike that.

11 As of December 21 when you sent this

12 e-mail to Ms. Landsberg, is it fair to say you

13 thought the nausea and vomiting story wasn't a

14 particularly good story? Is that fair to say?

15 MR. PHILLIPS: Object to the form.

16 A. No.

17 Q. Did you think it was a good story?

18 MR. PHILLIPS: Object to the form.

19 A. No.

20 Q. You thought that what you were seeing in the

21 nausea and vomiting in the 114 trial was a

22 cause of concern, correct?

23 MR. PHILLIPS: Object to the form.

24 A. I don't think so.

25 Q. So when we read your e-mail to Ms. Landsberg

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 here you're not expressing any -- is it fair to
2 say you're not expressing any concern, not
3 reflecting any concern about the nausea and
4 vomiting that was being experienced in the 114
5 trial?

6 MR. PHILLIPS: Object to the form.

7 A. Correct.

8 Q. Well the e-mail to Ms. Landsberg says: This is
9 blinded.

10 By saying this is blinded, did you mean
11 that the information, when it was finally
12 unblinded, could cause you to have a different
13 conclusion than the one that you listed here?

14 A. I don't know that I could infer that.

15 Q. When you wrote that the database is not clean,
16 did you mean that when the database was finally
17 cleaned up after the trial had been ended that
18 you might get different data?

19 A. Yes.

20 Q. Did you think you might get better data, more
21 positive data?

22 MR. PHILLIPS: Object to the form.

23 A. No.

24 Q. When you said: This is the one and only
25 titration scheme we tested. There will be

1 commercially very viable titration schemes

2 other than this one that will result in lower

3 AE rates.

4 What did you mean by that?

5 A. I don't know.

6 Q. Did you mean that the adverse event rates that

7 were being observed in the 114 trial probably

8 were not commercially viable, but that you

9 thought there might be other titration schemes

10 that Abbott could try that could result in more

11 commercially viable product?

12 MR. PHILLIPS: Object to the form.

13 A. I don't know.

14 Q. Is that a fair inference from what is written

15 here?

16 A. I don't think so.

17 Q. What do you believe you meant when you wrote

18 this in December 2000, as you sit here today?

19 MR. PHILLIPS: Object to the form.

20 A. That if the risk/benefit, given all the data,

21 didn't suggest that better tolerability for a

22 given efficacy was desirable that we would try

23 to improve that relationship by trying other

24 titration schemes.

25 Q. Did you believe as of December 2000 that in

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 order to come up with a commercial viable
2 product you were going to have to try a
3 different titration scheme that resulted in a
4 lower adverse event rate?

5 A. I don't know what I thought at that time.

6 Q. You go onto say: This is not the rate of
7 nausea and vomiting for ABT-594 at launch.

8 Do you see that?

9 A. Yes.

10 Q. When you wrote this, was it your intention to
11 reassure Ms. Landsberg that you thought you
12 would likely get a lower rate of nausea and
13 vomiting from ABT-594 at the launch?

14 A. I don't know.

15 Q. Do you recall any discussions with
16 Ms. Landsberg about the subject matter of this
17 e-mail?

18 A. No.

19 Q. Do you recall any discussions with Dr. Silber
20 about the subject matter of this e-mail?

21 A. No.

22 Q. Do you recall Ms. Landsberg expressing concern
23 at any point in time that the nausea and
24 vomiting rates that were being observed in the
25 114 trial before that data was unblinded was

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 going to adversely impact the commercial

2 viability of ABT-594?

3 A. No.

4 Q. Never heard her say that?

5 A. I don't know.

6

7 (At which time, Plaintiff's Exhibit

8 93 was marked for identification by the

9 Court Reporter.)

10

11 Q. Dr. McCarthy would you look at Exhibit 93 and

12 tell me if you've seen this document before?

13 A. Yes, in preparation with Mr. Phillips.

14 Q. Did you see it before that?

15 A. No, not that I remember.

16 Q. This appears to be an email from you to Dr.

17 Silber attaching a Purdue presentation. Do you

18 see that?

19 A. Yes.

20 Q. Where did you get the Purdue presentation back

21 in December 2000?

22 A. I don't know. These, generally what look like

23 power point slides, were slides used over the

24 course of years in internal Abbott discussions.

25 Q. This one is titled Purdue presentation,

1 correct?

2 A. Yes.

3 Q. And if you look at the slide file name is

4 ABT-594 Purdue 12/10?

5 A. The file name says that. I don't know what the

6 presentation name is titled.

7 Q. Do these slides look familiar to you?

8 A. Yes.

9 Q. If you take a look at the third slide under

10 ABT-594 overview?

11 A. Yes.

12 Q. The last line says: Phase II-B status. Do you

13 see that?

14 A. Yes.

15 Q. What information was supplied in conjunction

16 with this slide concerning Phase II-B status

17 and ABT-594?

18 MR. PHILLIPS: Objection to the

19 form.

20 A. I don't know.

21 Q. Did you ever participate in any presentation

22 using these slides?

23 A. Yes.

24 Q. And the occasions that you participated in

25 presentations using these slides, what

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

- 1 information did you provide about the Phase
2 II-B status of ABT-594?
3 A. I don't remember. I guess I should clarify, I
4 mean slides as in these individual slides. I
5 don't remember if I ever gave this particular
6 collection of slides as a presentation, yet
7 they are all familiar slides.
8 Q. Are you familiar with an entity named Purdue
9 Pharma?
10 A. Yes.
11 Q. In fact they have an office here in
12 Connecticut?
13 A. I don't know where they are located.
14 Q. Did you meet anyone from Purdue Pharma?
15 A. I think I have. I don't know why I have that
16 recollection, but I think I have.
17 Q. Have you ever had any business meetings with
18 anyone from Purdue Pharma?
19 A. That I don't remember.
20 Q. Do you know Mr. James Dolan from Purdue Pharma?
21 A. No.
22 Q. That name is not familiar to you?
23 A. No.
24 Q. Have you ever had any business meetings with
25 anyone at Pharmacia?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Do you recall when that occurred?

2 A. No.

3 Q. Do you recall at some point in time that Abbott

4 had cut back funding for ABT-594 to only six

5 months of activity?

6 A. No.

7 Q. Can you take a look at the e-mail that begins

8 at the bottom of page two in Exhibit 98 and

9 goes onto page 3. There is another e-mail from

10 Mr. Biarnesen to Ms. Hightower dated January

11 12.

12 Do you see that?

13 A. Yes.

14 Q. And it says: As per the assumption memo, we

15 are only funded for the completion of M99-114

16 and up to a go/no go decision at the end of

17 June.

18 Do you see this?

19 A. Yes.

20 Q. Did you learn at some point in time that Abbott

21 cut back funding for ABT-594 so it was funded

22 only for the completion of the 114 study and a

23 go/ no go decision?

24 A. I don't remember.

25 Q. Do you have any reason to doubt as you sit here

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 today that this information is correct?

2 A. No, other than not remembering it, but

3 generally typical of Abbott and any company to

4 fund things to a milestone.

5

6 (At which time, Plaintiff's Exhibit

7 99 was marked for identification by the

8 Court Reporter.)

9

10 Q. Dr. McCarthy you have what's been marked as

11 Exhibit 99. Would you look at the document for

12 a moment and tell me if you have seen it

13 before?

14 A. Not that I remember.

15 Q. It's entitled Analgesia Venture 2001 plan,

16 revised 1/26/01 and addressed to you, Dr.

17 Silber, Dr. Leonard and others at Abbott. Do

18 you see that?

19 A. Yes.

20 Q. Do you recall receiving financial plans for

21 ABT-594 and other compounds in the Analgesia

22 Venture?

23 A. Yes.

24 Q. The second page of the document makes reference

25 to the 2001 PLAN Review (Pass II). What does

1 that mean?

2 A. I don't know.

3 Q. Do you recall that Abbott periodically updated

4 its plans for spending for compounds?

5 A. Yes.

6 Q. Does this document reflect one of those revised

7 plans?

8 MR. PHILLIPS: Object to the form.

9 A. I don't know.

10 Q. If you look at the top of the page of

11 exhibit -- I think it's the fourth page of

12 Exhibit 99, the one with the bates number that

13 ends in 3359. It says: ABT-594 2001 PLAN KEY

14 STATISTICS PASS II?

15 A. Yes.

16 Q. Does this represent the key statistics of

17 ABT-594 as of January 2001?

18 MR. PHILLIPS: Objection, lack of

19 foundation. Object to form.

20 A. I don't know.

21 Q. Under key milestones and assumptions there are

22 a number of items there and dates. Do you see

23 that?

24 A. Yes.

25 Q. One of them is, for example, go, no go,

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Why was it you held this discussion?

2 A. I don't remember.

3 Q. Were you instructed to hold this discussion?

4 A. I don't remember.

5 Q. Why was it you were focusing on titration at

6 that particular point this time?

7 A. I don't remember at that particular point in

8 time.

9 Q. Why were you doing it before the results of the

10 114 study had been unblinded?

11 A. We had been talking about titration schemes

12 since the beginning of the project.

13 Q. Was there anything about the 114 study that

14 caused you to pay more attention to titration

15 schemes?

16 A. Not incrementally until the results were

17 available.

18 Q. Abbott never increased it's attention to coming

19 up with a titration scheme for ABT-594 before

20 the results of the 114 study were unblinded?

21 A. I would say in retrospect it was nearly a

22 constant level of attention throughout all of

23 the years from the very first study.

24

25 (At which time, Plaintiff's Exhibit

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 103 was marked for identification by the

2 Court Reporter.)

3

4 Q. Dr. McCarthy you have what's been marked as

5 Exhibit 103. Have you seen this before?

6 A. I don't remember if I have -- yes I have in

7 preparation with Mr. Phillips.

8 Q. It appears to been an e-mail from you to a

9 variety of people at Abbott including Dr.

10 Silber and Ms. Verlinden and others concerning

11 a strategy for ABT-594 NNR tolerability. Do

12 you see that?

13 A. Yes.

14 Q. You would agree with me that as of February of

15 2001 Abbott was increasing in it's trying to

16 address tolerability issues associated with NNR

17 and ABT-594?

18 A. Again I don't know if I would say increase.

19 Q. Well the first paragraph of this email says:

20 Please note the scientific strategy for ABT-594

21 NNR tolerability meeting to take place

22 tomorrow. This meeting is a follow on to the

23 Leiden review in which a recommendation was

24 heard for a comprehensive strategy to address

25 tolerability issues related to NNR's for pain,

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 including ABT-594's and follow-ons.

2 Do you see that?

3 A. Yes.

4 Q. Prior to the time you sent this e-mail out did

5 Abbott have a comprehensive strategy to address

6 tolerability with issues associated with NNR's

7 and ABT-594?

8 MR. PHILLIPS: Objection to the

9 form.

10 A. I don't know how to define comprehensive

11 strategy in this case.

12 Q. Your e-mail seems to indicate that you're going

13 to be trying to come up with a comprehensive

14 strategy to address tolerability issues

15 associated with ABT-594 and NNR's.

16 Do you see that?

17 A. Yes.

18 Q. Would you be trying to put together such a

19 comprehensive strategy in February of 2001 if

20 you already had one?

21 MR. PHILLIPS: Objection to the

22 form.

23 A. No.

24 Q. Is that something Dr. Leiden asked you to do?

25 MR. PHILLIPS: Object to the form.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 A. I don't know.

2 Q. That would appear to be what's indicated in the

3 email, you would agree with me on that point?

4 MR. PHILLIPS: Objection to the

5 form.

6 A. Yes.

7 Q. Do you know why it was that Dr. Leiden thought

8 it necessary in February of 2001 for Abbott to

9 put together a comprehensive strategy to

10 address tolerability issues associated with

11 ABT-594 and other NNR's?

12 MR. PHILLIPS: Object to the form,

13 assumes facts not in the record.

14 A. I don't know.

15 Q. Dr. McCarthy, is it fair to say when you wrote

16 emails to your compatriots back in the February

17 2001 time frame, you tried to include what you

18 understood to be accurate information?

19 A. I would assume.

20 Q. So you wouldn't say in this e-mail that in a

21 follow on review with Dr. Leiden there was a

22 recommendation made for Abbott to come up with

23 a comprehensive strategy to address

24 tolerability issues related to NNR's for pain

25 including ABT-594 unless that was true, right?

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 MR. PHILLIPS: Object to the form.

2 A. Yes.

3 Q. Had you ever had ABT-594 NNR tolerability

4 meetings prior to February 2001?

5 A. I don't know about meetings. Discussions, yes.

6 Q. Had you ever had meetings specific to

7 tolerability issues involving ABT-594 and NNR's

8 specifically?

9 A. I believe so.

10 Q. So the ABT-594 NNR tolerability meeting that's

11 referenced in this email was not the first such

12 meeting?

13 A. On that topic, no.

14 Q. How frequently had Abbott had meetings focused

15 on tolerability of ABT-594 prior to February

16 2001?

17 MR. PHILLIPS: Object to the form.

18 A. I don't know.

19 Q. Do you recall any such meetings?

20 A. Not particularly.

21 Q. What occurred at this meeting?

22 A. I don't remember.

23 Q. Who is Howard Cheskin?

24 A. He was an employee with an expertise in

25 formulations.

1 brochure gives little technical detail.

2 Do you see that?

3 A. Yes.

4 Q. What investigator brochure is Dr. Andrews
5 referring to there?

6 MR. PHILLIPS: Objection to the
7 form.

8 A. I don't know. I can only infer it's ABT-594
9 investigators brochure.

10 Q. What is an investigator brochure?

11 A. It's a document that summarizes in particular
12 the safety and pre-existing clinical data on a
13 compound for use for investigators and IRD's in
14 investigating the appropriateness of a clinical
15 trial and authorizing a study to take place at
16 a given site.

17 Q. Was there anyone at the meeting with Dr.
18 Andrews who was there to provide information
19 about the ongoing 114 study?

20 A. I don't remember.

21

22 (At which time, Plaintiff's Exhibit

23 107 was marked for identification by the

24 Court Reporter.)

25

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. Dr. McCarthy, you have Exhibit 107. Have you

2 seen this document before?

3 A. I don't recall it.

4 Q. It appears to be a string of e-mails, one from

5 a Mr. James Dolan@Pharma.com but appears to be

6 from Purdue Pharma to Mr. Weiland and then Mr.

7 Weiland back to Mr. Dolan and Dr. Silber

8 forwarding the string of emails on to you among

9 others at Abbott.

10 Do you see that?

11 A. Yes.

12 Q. Do you have a recollection of receiving the

13 e-mails in early March 2001?

14 A. No.

15 Q. On the bottom of page 1 and to the top of page

16 2 page, Mr. Dolan's email of March 6, 2001,

17 this states among other things: Purdue would

18 not be able to commit to any commercial terms

19 now before the M99-114 data were available.

20 Do you see that?

21 A. Yes.

22 Q. Was any data regarding the 114 study shared

23 with representatives of Purdue before that data

24 was unblinded?

25 MR. PHILLIPS: Object to the form.

1 A. I don't know.

2 Q. Do you know after the data was unblinded

3 whether any of it was shared with

4 representatives of Purdue Pharma?

5 A. Not to my knowledge.

6 Q. Do you recall learning in 2001 Purdue Pharma

7 would not move forward with any discussions to

8 co-develop or partner on ABT-594 before the 114

9 data was unblinded?

10 A. I don't remember.

11 Q. Do you recall any discussions with anyone at

12 Abbott on this topic?

13 A. No.

14 MR. DAVIS: While don't we go off

15 the record for a moment.

16

17 (At which time, there was a short

18 recess taken by the parties.)

19

20 (At which time, Plaintiff's Exhibit

21 108 was marked for identification by the Court

22 Reporter.)

23

24 BY MR. DAVIS:

25 Q. Dr. McCarthy you have what's been marked

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 terminate. Do you see that?

2 A. Yes.

3 Q. Were you aware that in early March 2001 Abbott

4 management regarded ABT-594 as a probable

5 terminate?

6 MR. PHILLIPS: Object to the form.

7 A. No.

8 Q. You didn't hear that at all in March 2001 time

9 frame?

10 A. No.

11

12 (At which time, a discussion was

13 held off the record.)

14

15

16 (At which time, Plaintiff's Exhibit

17 111 was marked for identification by the

18 Court Reporter.)

19

20 BY MR. DAVIS:

21 Q. Dr. McCarthy you have Exhibit 111 in front of

22 you. Have you seen this document before?

23 A. Yes -- well at least something that looks

24 familiar to this or similar to this in

25 preparation with Mr. Phillips.

1 112 was marked for identification by the
2 Court Reporter.)

3 Q. Dr. McCarthy, as you sit here today do you have
4 a greater recollection of the presentation that
5 was made by Dr. Andrews or the discussion at
6 that presentation than you had when we last
7 met?

8 A. No, other than a vivid recollection of the room
9 we were actually in, which remains intact and
10 that the presentation lodged in my memory is a
11 highly generic one in that it was somewhat
12 disappointing in that it was not very helpful
13 for us.

14 Q. You have in front of you Exhibit 112. Have you
15 seen this document before?

16 A. Not that I remember -- I don't remember seeing
17 it before.

18 Q. Would you take a moment and read it and tell me
19 when you're done?

20 A. I'm done.

21 Q. Do you recall -- let me go back for a moment.

22 Who is Judith Brownell, if you know?

23 A. I don't know her.

24 Q. Do you know Susan Nunn?

25 A. Yes, I think she was part of the data

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Do you know of anyone who was pushing to
2 break the blind on the 114 study back in March
3 of 2001?

4 A. Generally everyone is looking for the blind to
5 be broken as soon as possible, so probably
6 myself and everyone on the team was trying to
7 do it as quickly as possible.

8 Q. Why was there -- the blind was going to be
9 broke at sometime in May or April, is that
10 right?

11 A. I don't remember the timing.

12 Q. Why were people trying to push up the blind?
13 What was the hurry?

14 A. Nothing specific to this project, across the
15 entire industry the sooner you know your
16 information, the sooner you can take action on
17 it

18

19 (At which time, Plaintiff's Exhibit

20 113 was marked for identification by the

21 Court Reporter.)

22

23 Q. Dr McCarthy you have Exhibit 113 which appears

24 to be some e-mails including one from doctor

25 Leonard to Ms. Verlinden and from Ms. Verlinden

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 to you. Is she a physician?

2 A. No she's a Ph.D and a PharmD, I think.

3 Q. The e-mail she wrote to you on May 8, 2001, do

4 you recall seeing this e-mail?

5 A. I don't.

6 Q. It's references 594 and she says: Dear all,

7 John has asked me to take on a role that is a

8 little more active and involved than I had

9 intended with regard to the design plan for

10 ABT-594.

11 Do you see that?

12 MR. PHILLIPS: I believe you said

13 the design plan, but it is to designing the

14 plan.

15 MR. DAVIS: I'm sorry.

16 Q. Let me reread it. It says: John has asked me

17 to take on a role that is a little more active

18 and involved than I had intended with regard to

19 designing the plans for ABT-594.

20 Did I read that correctly this time?

21 A. Yes.

22 Q. Do you recall Ms. Verlinden taking on that role

23 at that time?

24 A. No.

25 Q. Later on in the same paragraph she says: As

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

- 1 you can see the compound has not been given up
- 2 on, but on the other hand it does not seem like
- 3 there is money available for it at this time.
- 4 Do you see that?
- 5 A. Yes.
- 6 Q. Did you understand that there was no funding
- 7 available for ABT-594 in May 2001?
- 8 A. I don't remember.
- 9 Q. And then in the next paragraph the next to last
- 10 line says: The issue we need to get to is we
- 11 want to obtain efficacy of three hundred
- 12 micrograms BID or better, but need to get
- 13 around the nausea and vomiting and hence the
- 14 horrendous dropout rates.
- 15 Did you agree with Ms. Verlinden's at that
- 16 time that the dropout rates experienced in the
- 17 114 study were horrific?
- 18 A. I don't know what I thought at that time.
- 19 Q. But you don't doubt that's what she's referring
- 20 to as horrendous dropout rates in the 114
- 21 study?
- 22 MR. PHILLIPS: Objection to the
- 23 form.
- 24 A. I'm not sure what she's referring to.
- 25 Q. At this point in time in early May 2001 results

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 of the 114 had been unblinded, correct?

2 A. I had forgotten the precise timing.

3 Q. We see that the e-mail from Dr. Leonard to

4 Ms. Verlinden dated 5/5/01. It says: I

5 briefly mentioned to the Ex Comm and showed to

6 Jeff the results from the Phase II study.

7 Do you see that?

8 A. Yes.

9 Q. Was there any other Phase II studies that had

10 results released in or around May 2001?

11 A. No.

12 Q. So that was the 114 study?

13 A. Yes.

14

15 (At which time, Plaintiff's Exhibit

16 114 was marked for identification by the

17 Court Reporter.)

18

19 Q. Dr. McCarthy you have Exhibit 114 in front of

20 you?

21 A. Yes.

22 Q. It appears to be an e-mail from you to

23 Ms. Verlinden dated May 21, 2001. Do you see

24 that?

25 A. Yes.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 and kept them in my office and almost certainly
2 they would have been -- I don't know what
3 happened to them after I left.

4 Q. Did you ever discuss with any of these advisors
5 the 114 trial before the data from the trial
6 was unblinded?

7 A. Probably. Almost certainly several of them
8 helped in designing the trial and writing the
9 protocol.

10 Q. Did you ever discuss with them the results of
11 the trial before the data was unblinded?

12 A. I don't know.

13 Q. These advisors were paid for their time?

14 A. Yes.

15

16 (At which time, Plaintiff's Exhibit

17 115 was marked for identification by the

18 Court Reporter.)

19

20 Q. Dr. McCarthy you have what's been marked as

21 Exhibit 115. Can you identify this document

22 for me?

23 A. It looks again like many of the slides that

24 were frequently used to describe 594 but it

25 looks like -- at one point I generally

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 remembered a proposal to try and further
2 explore 594's potential after we had the 114
3 results. This may have been some presentation
4 or some background material related to that.

5 Q. Why did you think it -- strike that -- did you
6 participate in the preparation of these slide
7 materials?

8 A. Almost certainly. I probably created these.

9 Q. And these are in September 2001?

10 A. Yes.

11 Q. Why at that time did you think Abbott should
12 consider conducting another Phase II-B study of
13 ABT-594?

14 A. I don't remember what the rationale at that
15 time was.

16 Q. Had the Phase II-B study, the 114 study
17 determined the maximum tolerated dose for
18 ABT-594?

19 A. I think the collection of studies over the
20 years determined what the maximum tolerated
21 dose was.

22 Q. What was the maximum tolerated dose for
23 ABT-594?

24 A. I don't know to be honest. I've forgotten what
25 that would probably best be described as for

1 594.

2 Q. That was the purpose of the study to determine

3 the maximum dose?

4 A. No, not per se.

5 Q. Is that not the reason why they did the dose

6 ranging study?

7 A. Maximum tolerated dose is generally -- really

8 is often something that's determined from the

9 earliest studies and has kind of a very very

10 narrow meaning of a dose at which a small

11 number of people just can't take a drug. At

12 later points like in the 114 study it's really

13 more about risk/benefit than maximum tolerated

14 dose.

15

16 (At which time, Plaintiff's Exhibit

17 116 was marked for identification by the

18 Court Reporter.)

19

20 Q. Dr. McCarthy you've been handed what's been

21 marked Exhibit 116. The top e-mail is from, I

22 believe Mr. Biarnesen to you among others at

23 Abbott dated October 24, 2001.

24 Do you see that?

25 A. Yes.

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. And then the top e-mail says: In a meeting
2 with Discovery, Commercial, Business
3 development, and the Venture, it was concluded
4 that ABT-594 will be a candidate for
5 out-licensing.

6 Do you see that?

7 A. Yes.

8 Q. Did you participate in that discussion?

9 A. I don't remember

10

11 (At which time, Plaintiff's Exhibit
12 117 was marked for identification by the
13 Court Reporter.)

14

15 Q. Looking again at Exhibit 116 do you have any
16 reason to doubt you received this e-mail in
17 October 2001?

18 A. No.

19 Q. In looking at Exhibit 117 would you read that
20 to yourself for a moment and tell me when
21 you're done?

22 A. I'm done.

23 Q. Who is Rene Allard?

24 A. I don't know.

25 Q. It appears to an inquiry you received -- or

McCarthy, Bruce Gerald (Linked) 03/16/2007 9:14:00 AM

1 Q. So it wasn't quite accurate to say it was in
2 phase II at that time. Development had been
3 stopped, right?

4 MR. PHILLIPS: Object to the form.

5 A. I don't know what I was trying to convey about
6 phase II. It might have been that in an
7 overall scheme that was it's point of
8 development

9

10 (At which time, Plaintiff's Exhibit

11 118 was marked for identification by the

12 Court Reporter.)

13

14 Q. Dr. McCarthy you have Exhibit 118. Would you
15 read the first e-mail from you to Ms. Verlinden
16 dated June 27, 2002 to yourself and tell me
17 when you're done?

18 A. I'm done.

19 Q. The e-mail from you to Ms. Verlinden had to do
20 with your goals for the upcoming year, correct?

21 A. It appears to be.

22 Q. And under the section New Goals there's a
23 reference to 594. Do you see that?

24 A. Yes.

25 Q. And you were telling Ms. Verlinden that one of

1 the upcoming goals was no longer applicable and

2 that was outlicensing of ABT-594. Do you see

3 that?

4 A. Yes.

5 Q. And you state: I'm in the process of verifying

6 that Dan Norbeck blocked the outlicense of 594.

7 What did you mean?

8 A. I don't know.

9 Q. At some point in time did you learn that

10 Mr. Norbeck had somehow blocked outlicensing of

11 ABT-594?

12 A. I may have, I don't remember.

13 Q. You have no recollection of that as you sit

14 here today?

15 A. No.

16 Q. Do you have a recollection of learning someone

17 within Abbott had blocked the outlicensing of

18 ABT-594?

19 A. No.

20 Q. Do you know why anyone would block the

21 outlicensing of ABT-594?

22 MR. PHILLIPS: Object to the form.

23 A. No.

24 Q. Did you in fact verify that Mr. Norbeck had

25 blocked the outlicensing of ABT-594?

1 A. No.

2 Q. Recall discussions with anyone at Abbott about

3 someone, Mr. Norbeck included, blocking the

4 outlicensing of ABT-594?

5 A. No

6

7 (At which time, Plaintiff's Exhibit

8 119 was marked for identification by the

9 Court Reporter.)

10

11 Q. Dr. McCarthy you have in front of you Exhibit

12 119. Can you identify this document for me?

13 A. No.

14 Q. Have you ever -- or did you ever see documents

15 like this when you worked at Abbott?

16 A. Not that I remember.

17 Q. Did you participate in a probability assessment

18 pertaining to ABT-594?

19 A. Yes.

20 Q. Do you recall when you did that?

21 A. No.

22 Q. Did you do it before ABT-594 development was

23 discontinued?

24 A. Yes.

25 Q. Did you do it back in the 2000 time frame?

1 A. I don't remember in 2000, per se.

2 Q. Do you recall providing your own assessment of
3 the probability of success of ABT-594?

4 A. I don't recall.

5 Q. When you participated in the process to come up
6 with a probability assessment for ABT-594 who
7 else assisted in that process?

8 A. At times the DSG group. That's the only
9 specific team I can think of.

10 Q. There are references to Chris and Bruce in this
11 document?

12 A. Yes.

13 Q. Is that a reference to Dr. Silber and you?

14 A. I believe so.

15 Q. Do you recall, while the 114 trial was still
16 underway, noting that SE's while apparent still
17 wouldn't stop the trial, however there was
18 significant drop outs still occurring.

19 Do you remember this?

20 A. I don't remember this.

21 Q. Do you recall discussing preliminary results of
22 the 114 trial in the course of a probability
23 assessment for ABT-594?

24 A. No.

25 Q. Was the probability assessment that you

McCarthy Deposition Exhibit 3

P's Exhibit BT



ABBOTT

Pharmaceutical Products Division

Bruce McCarthy, M.D.
Associate Medical Director
Analgesia Venture

D-48Q, AP34
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Tel: (847) 935-6244
Fax: (847) 938-5258

March 12, 1999

Michael Meyer, Ph.D.
Cholinergic Modulation
Department: 47W
Building: AP10

Dear Michael,

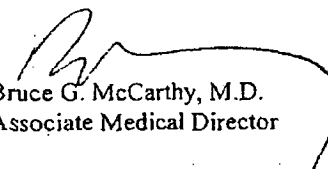
Enclosed is a copy of the packet sent to the advisors, who are attending the ABT-594 European Advisory Meeting. It includes an ABT-594 Overview, Meeting Goals, Issues to Prepare, an agenda, the ABT-594 Investigator Brochure (not included for Abbott attendees) and abstracts of two clinical trial protocols.

Please note that we will not be discussing the specific results of the molar extraction trial with the advisors. Instead, the advisors have several drug profiles to consider as the basis for discussions. While ABT-594 has attributes that must be considered in the design of a coherent development program, I believe the advisors may focus unnecessarily on ABT-594's performance in the molar extraction trial. As a result, we may lose some valuable understanding of analgesic drug development in Europe that may be applicable for follow-on compounds (such as ABT-259) or other classes of drugs (adenosine kinase inhibitors).

I will offer that a molar extraction trial has recently been completed, but the data is not yet available. Profile B in the enclosure, however, includes the major results of the molar extraction study.

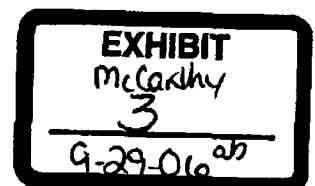
Please come to the meeting armed with all your questions. I want everyone to leave the meeting satisfied!

Sincerely,


Bruce G. McCarthy, M.D.
Associate Medical Director

BGM/ckk

encl



HIGHLY
CONFIDENTIAL

ABBT 0024357

March 12, 1999

ABT-594 Overview

Status and future of ABT-594

Phase I

Phase I studies started in July, 1997. Several Phase I trials have been conducted to assess pharmacokinetics, bioavailability and tolerability. The major finding of these studies is that nausea, vomiting and dizziness are the primary dose-limiting adverse events. They become most apparent at doses of 100 µg or higher. Patients who have eaten a meal prior to dosing have improved GI tolerability; this effect is not related to altered pharmacokinetics (PK is similar in fed and fasted states). The maximally tolerated dose is somewhere slightly above 100 µg for fasted patients and 150 µg for fed patients. Phase I trials have been conducted using two different formulations: a solution and a soft elastic capsule.

Phase II

Pre-clinical experiments suggested ABT-594 is efficacious in a variety of pain states (including acute and chronic nociceptive, and neuropathic pain). In order to bridge pre-clinical and clinical experiments, three key clinical states have been targeted: pain after molar extraction, pain associated with osteoarthritis of the knee, and pain associated with peripheral neuropathy. The trial in molar extraction was recently completed and the trials in osteoarthritis of the knee and in neuropathic pain are ongoing. The molar extraction study was of standard design and used a single dose of a solution (either 25, 50, 75 or 100 µg) after moderate or severe pain developed. The osteoarthritis and neuropathic pain trials are of short duration (3 weeks) and use twice-daily dosing regimens of a soft elastic capsule (25, 50, 75 µg BID). Portions of these protocols are in this enclosure.

Phase III

Phase III will be initiated depending upon the results of the Phase II program. Specifically, Phase III will include osteoarthritis and/or neuropathic pain if ABT-594 is efficacious in Phase II. Trial designs (used in Phase II) will need to be modified for Phase III (e.g. duration of osteoarthritis studies will be longer). In the United States, the target indications would be for the treatment of pain associated with osteoarthritis and for the treatment of neuropathic pain.

Product Profiles

The profile of ABT-594 will be better defined by data from the molar extraction, osteoarthritis and neuropathic pain trials. Until those data are available, please consider the following possible profiles of ABT-594 as the basis of discussion:

Profile A

In molar extraction, ABT-594 has onset (significant difference from placebo) by 15-30 minutes and is comparable to ibuprofen 400 mg (ibuprofen 400 mg is the gold standard in this model). The osteoarthritis Phase II study suggests that ABT-594 will have equal or better efficacy than the

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gold standard treatment for pain associated with osteoarthritis. In the neuropathic pain Phase II study, ABT-594 is not different than placebo.

Profile B

In molar extraction, ABT-594 has onset (significant difference from placebo) at two hours and is effective (different than placebo). In osteoarthritis, the phase II study suggests that ABT-594 will have equal or better efficacy than the gold standard treatment for osteoarthritis pain. In the neuropathic pain Phase II study, ABT-594 is significantly better than placebo.

In addition, please consider an additional drug profile. Abbott is developing other novel classes of analgesic drugs. This profile includes the added property of anti-inflammation. The drug (drug X), exerts its analgesic and anti-inflammatory activities through adenosine kinase inhibition.

Profile C

In molar extraction, the drug X has onset (significant difference from placebo) by 15-30 minutes and is comparable to ibuprofen 400 mg (ibuprofen 400 mg is the gold standard in this model). In osteoarthritis, drug X has equal or better efficacy than the gold standard treatment for osteoarthritis pain. It is ineffective for neuropathic pain. In addition, drug X provides anti-inflammatory activity similar to high dose naproxen.

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Abbott Laboratories European Development Advisory Board Meeting
 Sheraton Hotel
 Amsterdam, Netherlands
 March 22 and 23, 1999

Agenda

Most sessions begin with a brief advisor presentation followed by a discussion. The basis for the advisor presentation can be found in the Issues To Prepare document.

Monday, March 22, 1999

11.00 - 12.00	Lunch - Voyager Restaurant
12.00 - 12.15	Introduction
12.15 - 15.00	Current Treatment Practices in Europe Neuropathic Pain - Dr. Martin Koltzenburg Osteoarthritis Pain - Prof. Dr. Leo Van de Putte Other Pain Types - Advisor Presentations
15.00 - 15.15	Break
15.15 - 16.15	Experimental Medicine Implications of ABT-594's Pharmacology in the Selection of Pain Types to Study in Clinical Trials Prof. Dr. Walter Zieglgänsberger Implications of ABT-594's Pharmacology for Other Non-pain Disorders
16.15 - 17.00	Adenosine Kinase Inhibition Elizabeth Kowaluk, Ph.D., Abbott Discovery
18.30	Reconvene in hotel lobby for shuttle pick-up
7:00 PM.	Dinner at the Excelsior Restaurant in Hotel De L'Europe

Tuesday, March 23, 1999

7.00 - 8.00	Breakfast - Voyager Restaurant
8.00 - 8.15	Introduction
8.15 - 9.15	ABT-594 Overview Michael Meyer, Ph.D. Bruce McCarthy, M.D. Laura Robinson, M.B.A.
9.15 - 10.30	Osteoarthritis Pain Trial Design Prof. Dr. Leo Van de Putte Prof. George Nuki
10.30 - 10.45	Break
10.45 - 12.00	Neuropathic Pain Trial Design Dr. Martin Koltzenburg
12.00 - 13.00	Lunch - Voyager Restaurant
13.00 - 15.00	European Development Strategy: Coordinating Clinical Development, Regulatory and Commercial Issues Advisor Presentations of Issues #5 and #6
15.00 - 15.15	Break
15.15 - 17.00	European Development Strategy, Continued

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Abbott Laboratories European Development Advisory Board
Sheraton Hotel & Convention Center
Amsterdam, Netherlands
March 22 and 23, 1999

Abbott Invitees:

Vicky Blakesley, M.D.
Abbott International

✓ Gordon Boyd, M.D.
Abbott International
Berkshire, UK

✓ James Doran, M.B.A.
New Product Development

✓ Rita Driscoll, M.D.
Analgesia Venture

Ruza Filipovic-Miler, M.D.
Abbott GmbH
Wiesbaden, Germany

James Gorman, M.D.
Abbott International

✓ Olga Jasinsky, M.B.A.
Analgesia Venture

✓ Elizabeth Kowaluk, Ph.D.
Neurological and Urological Diseases
Research (NUDR)

✓ Nigel Livesey, M.D.
Abbott International

✓ Bruce McCarthy, M.D.
Analgesia Venture

✓ Michael Meyer, Ph.D.
Cholinergic Modulation

✓ Laura Robinson, M.B.A.
Abbott International

✓ David Ross, PharmD., M.B.A.
Regulatory Affairs

✓ Christopher Silber, M.D.
Analgesia Venture

✓ Sunil Soni, M.D.
Abbott International
Berkshire, UK

James Sullivan, Ph.D.
Neurological and Urological
Diseases Research (NUDR)

✓ Michael Williams, Ph.D., D.Sc.
Neurological and Urological
Diseases Research (NUDR)

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March 12, 1999

Meeting Goals

Our primary goals for the Advisory Meeting are as follows:

Understand the current practice of the treatment of pain in its various presentations (especially in osteoarthritis and neuropathic pain).

Understand how practice varies by country, region, and setting (hospital, office, specialist, generalist).

Understand how current drugs are used and problems associated with them.

Understand how currently available drugs are priced and how price and reimbursement affects treatment decisions.

Understand the unmet needs in the treatment of pain.

Understand the study design for Phase III analgesic trials (especially in osteoarthritis and neuropathic pain).

Understand the regulatory issues associated with analgesic drug approval.

Understand the types of indications possible (for the treatment of pain, for the treatment of osteoarthritis pain/neuropathic pain, etc.).

Understand the best choice of target indications such that the drug is available to the most people for whom it may provide benefit as soon as possible (development strategy).

Understand specific regulatory requirements to achieve a specific claim (especially osteoarthritis and neuropathic pain).

Understand pharmacoeconomic studies required for approval and pricing.

Understand implications of ABT-594's pharmacology on rational clinical development.

Understand implications of adenosine kinase inhibition as a mechanism of analgesia.

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March 12, 1999

Issues to Prepare

Please come to the meeting prepared to give a 3-5 minute presentation on the following topics. Most sessions (see Agenda) will begin with an advisor presentation as a starting point for discussion.

1. If you regularly treat neuropathic pain, discuss your approach to and treatment of neuropathic pain. What are the types of neuropathic pain? What prescription and non-prescription treatments are available? Who treats these patients (specialists, generalists)? What is the gold standard therapy for various types of neuropathic pain? What represents a significant improvement in safety and efficacy vs. gold standard therapy to change from the gold standard therapy?
2. If you regularly treat osteoarthritis pain, discuss your approach to and the treatment of osteoarthritis pain (knee, hip). What prescription and non-prescription treatments are available? Who treats these patients (specialists, generalists)? What is the gold standard therapy for osteoarthritis pain? What represents a significant improvement in safety and efficacy vs. gold standard therapy to change from the gold standard therapy?
3. Choose an additional pain state that you treat regularly (e.g. post-operative pain, dysmenorrhea, lower back pain) and discuss your approach and treatment of it (as in questions 1 and 2).
4. Discuss future drugs (currently not available, but will be available within five years) that could change your answers for 1, 2, and 3.
5. If you were developing ABT-594, which pain states would you study in clinical trials? Why? Will the pain states you choose result in the approval of ABT-594 such that it will be available to the most people for whom the drug may benefit as soon as possible?
6. Review the pain states you chose in question five. Choose one and describe the key elements of a study of that pain state: study design, population to study, instruments/scales, endpoints, duration, comparators.

The following question was addressed to Prof. Nuki and Prof. Van de Putte only

7. Describe the key elements of a study of pain associated with knee OA (and hip OA): study design, population to study, instruments/scales, endpoints, duration, comparators.

The following questions were addressed to Dr. Koltzenburg only

7. Describe the key elements of a study of pain associated with distal symmetric polyneuropathies: study design, population to study, instruments/scales, endpoints, duration, comparators.
8. What other neuropathic pain states would you study? Why? Describe study designs to evaluate ABT-594 in these other neuropathic pain types.

The following question was addressed to Prof. Ziegler-Schäfer

7. Based on pre-clinical data, in which clinical pain states is ABT-594 likely to be effective? Why?

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Abbott Laboratories European Development Advisory Board
Sheraton Hotel & Convention Center
Amsterdam, Netherlands
March 22 and 23, 1999

Invitations Sent To:

Professor François Boureau
Hospital Saint-Antoine
Paris, France

✓ Professor Marcel Chauvin
Hospital Ambroise Paré
Boulogne, France

Professor Paul Dieppe
University of Bristol
Bristol, UK

Professor Maximie Dougados
Hospital Cochin
Paris, France

✓ Professor Maria Adele Giamberardino
University of Chieti
Chieti, Italy

Professor Magdi Hanna
King's Healthcare
London, UK

Professor Troels S. Jensen
Aarhus University Hospital
Aarhus C, Denmark

✓ Professor Eija Kalso
Helsinki University Central Hospital
Helsinki, Finland

✓ Professor Martin Koltzenburg
University of Würzburg
Würzburg, Germany

Professor Klaus A. Lehmann
University of Cologne
Cologne, Germany

Professor Henry McQuay
Churchill Hospital
Oxford, UK

Professor Luis Miguel Torres Morera
Anestesia Reanimación y
Tratamiento del Dolor
Jefe de Servicio
Cádiz, Spain

✓ Professor Leo Van de Putte
University Hospital Nijmegen
Nijmegen, Netherlands

Professor Leonardo Vecchiet
Semeiotica Medica
Chieti Scalo (CH), Italy

✓ Professor Walter Zieglgänsberger
Max Planck Institute of Psychiatry
München, Germany

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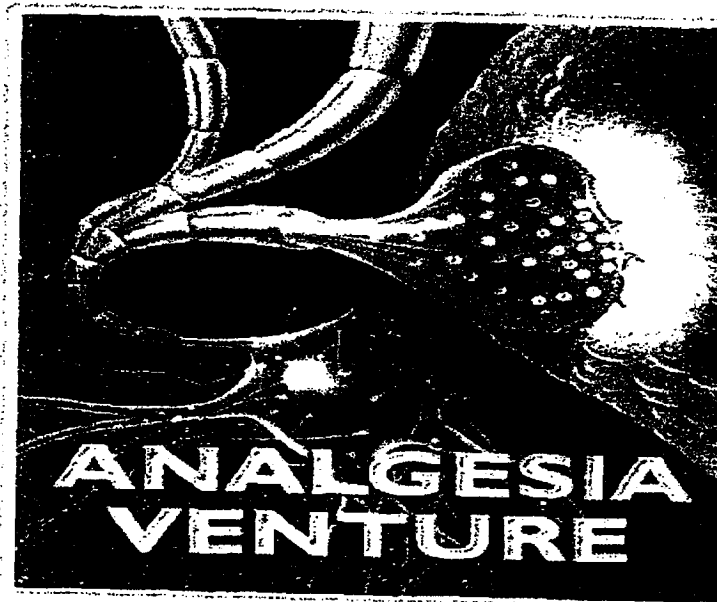
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McCarthy Deposition Exhibit 6

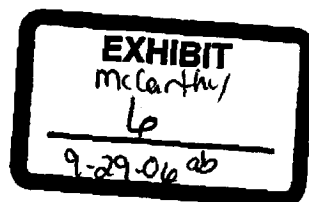
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Part 1

ABT-594 DEVELOPMENT PLAN



June, 1999



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ABT-594

EXECUTIVE SUMMARY

June, 1999

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6668-R2

Analgesia Venture (6/23/99)
Development Plan
ABT-594

Table of Contents

	Page
A. Executive Summary	1
A.1 Introduction	1
A.1.1 The Disease Class	1
A.1.2 Drug Class and Pharmacological Characteristics	1
A.2 Commercial	3
A.2.1 ABT-594 Target Profile - Indication	3
A.2.2 Forecast	4
A.3 Clinical Development	6
A.3.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies	6
A.3.2 Cost Through NDA	7
A.3.3 Development Milestones	8

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

1

A. EXECUTIVE SUMMARY

A.1 Introduction

A.1.1 The Disease Class

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at \$100 billion a year in direct and indirect costs. Approximately 95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain. Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

A.1.2 Drug Class and Pharmacological Characteristics

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 is anticipated to be effective for the treatment of both acute and neuropathic pain. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

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Development Plan
ABT-594

2

ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. *In vitro* and *in vivo* studies show that the antinociceptive actions of ABT-594 are blocked by nicotinic acetylcholine receptor (nAChR) antagonists, but not by opioid receptor antagonists supporting a mechanism of action that involves nAChR modulation.

ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes. ABT-594 also selectively prevents the activation of dorsal horn neuron responses to noxious mechanical and thermal stimuli, without having effects on non-noxious mechanical and thermal stimuli that could impair sensory perception.

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Development Plan
ABT-594

3

A.2 Commercial

A.2.1 ABT-594 Target Profile

PFCC/BDC Profile (12/18/97)	Current Profile (6/23/99)	Rationale for Profile Change	Probability	Status	Share Impact
Indicated for the treatment of pain (general pain claim)	Indicated for the treatment of osteoarthritis pain	"General pain" claim not achievable due to slow onset of action; proof of principle established in molar extraction study	Medium	9/99, 1Q01	High
Effective in neuropathic pain	Indicated for the treatment of neuropathic pain	Indication specific claims now favored since general pain claim not achievable	Low	9/99, 2Q01	Medium
Effective for moderate to moderately-severe pain	N/A	No longer applicable without general pain claim	N/A	N/A	N/A
Not scheduled	No change	N/A	High	4Q02	High
Improved safety profile compared to opioids including: - less GI motility impairment - less respiratory depression - low tolerance potential - no dependence/withdrawal	No clinically significant tolerance, dependence or withdrawal	Simplify profile to focus on the most commercially important AEs	Medium	2Q01	High
	Very few abnormal LFTs	Abnormal LFTs in a few Phase I subjects	High	9/99	High
	Very low nausea/vomiting at effective dose	Relatively high incidence of nausea/vomiting in single dose Phase I & II subjects (food and dose dependent)	Medium	9/99	High
	Other safety OK	Simplify profile	Medium	9/99, 2Q01	High
	No significant or sustained differential efficacy in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	Low	9/99, 2Q01	High
	No significant or sustained differential side effect profile in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	High	9/99, 2Q01	Medium
	No re-initiation of cravings in ex-nicotine users	Possible due to nicotinic mechanism	Medium	2Q01	High

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Development Plan
ABT-594

4

A.2.1 ABT-594 Target Profile (Continued)

PFCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Onset of action in less than 30 minutes	Onset of action comparable to other therapies used to treat OA	Onset of action estimated at 90 minutes in Phase II trial	Low	9/99	Medium
	Onset of action comparable to other therapies used to treat neuropathic pain	Onset of action estimated at 90 minutes in Phase II trial	High	9/99	Medium
BID/TID dosing	BID dosing	Competitive dynamics highlight importance of dosing convenience	High	9/99	Medium
No major drug interactions, especially with drugs used for common chronic conditions	No change	N/A	High	4Q00	Medium

A.2.2 Forecast

U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rxs (MM)	280	285	291	297	303
- % chg	2%	2%	2%	2%	2%
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rxs (MM)	2.8	7.1	11.1	13.3	15.1
Price/Rx (\$)	34.97	35.67	36.39	37.12	37.86
Abbott Sales (\$MM)	125	254	402	495	573
R&D (\$MM)	5	5	4	4	3
SG&A (\$MM)	66	98	90	85	84
SMM (%)	97.2	97.3	97.3	97.4	97.4
Div. Margin (\$MM)	59	162	324	427	509

10 year pre-tax NPV @ 12.5% = \$1.016 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$587 MM

10 year post-tax ENVY @ 12.5% = TBD

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Development Plan
ABT-594

5

Key assumptions:

- Assumes 12/97 PPCC profile
- NDA Filed 12/01, Launch 6/03
- First in class ChCM
- Usage = 70% chronic and 30% acute
- Weighted average days per Rx = 15.6
- Stocking at 12% of first year's sales
- Detailing includes 30% of IMs, 25% of FPs and GPs, 25% of Rheumatologists, and 10% of Neurologists
- Sampling at 80% of details at launch, 8 units per detail, 5 days of therapy per unit
- Patent expires 12/2016

Forecast Update Plan:

Forecast will be updated in late June/early July 1999 to account for revised indications of OA and/or neuropathic pain and the associated spillover use in other pain states.
Forecast will be available well in advance of ABT-594 Go/No Go decision in 9/99.

Ex-U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rx's (MM)	-	-	-	-	-
- % chg					
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rx's (MM)	-	-	-	-	-
Price/Rx (\$)	-	-	-	-	-
Abbott Sales (\$MM)	60	150	250	300	320
R&D (\$MM)	3.4	3.2	2.8	2.4	2.0
SG&A (\$MM)	27	53	50	48	45
SMM (%)	95%	95%	95%	95%	95%
Div. Margin (\$MM)	26	85	182	235	251

10 year pre-tax NPV @ 12.5% = \$428

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$253

10 year post-tax ENVY @ 12.5% = TBD

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Development Plan
ABT-594

6

Key assumptions:

- First in class ChCM
- Indicated for treatment of moderate to moderately-severe pain
- Effective in neuropathic pain
- Good tolerability and safety profile
- No nicotinic effects
- Launched in all AI regions, including Japan, simultaneously (2003)

Forecast Update Plan:

- Forecast will be updated 9/99 (in time for the Go/No Go decision) to reflect results of marketing research to be conducted 3Q 1999 regarding expected uptake of 594 in OA and neuropathic pain markets, as well as potential spill-over prescribing for other pain states.

Global Forecast

	2003	2004	2005	2006	2007
U.S. Sales (\$MM)	125	254	402	495	573
Ex-U.S. Sales (\$MM)	60	150	250	300	320
Total Sales (\$MM)	185	404	652	795	893
Total Division Margin (\$MM)	85	247	506	662	760

10 year pre-tax NPV @ 12.5% = \$1.44 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$840 MM

10 year post-tax ENVY @ 12.5% = TBD

A.3 Clinical Development

A.3.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Given the spectrum of analgesic activity of ABT-594 in preclinical animal models of pain, the clinical development program for ABT-594 will evaluate the safety and efficacy of ABT-594 for the treatment of neuropathic pain and pain associated with osteoarthritis. In addition, pilot studies are planned to assess the safety and efficacy of ABT-594 for the treatment of pain associated with cancer.

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Development Plan
ABT-594

7

Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Indication (Study Type)	Phase II		Phase III		Phase IIIb	
	# Studies	# Patients	# Studies	# Patients	# Studies	# Patients
Osteoarthritis						
U.S.	1 ^c	250	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Neuropathic Pain						
U.S. ^a	1 ^c	150	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Cancer Pain						
U.S.	2	500	-	-	-	-
Long-Term Safety						
U.S.	-	-	1 ^a	600 ^d	-	-
Europe	-	-	1 ^a	300 ^d	-	-
Pricing Studies						
U.S.	-	-	-	-	1	500
Europe	-	-	-	-	1	500
Canada	-	-	-	-	1	500
Australia	-	-	-	-	1	500
TOTAL	4	900	12	5400	4	2000

a. Registration Trial

b. Bridging Study

c. Ongoing

d. Patients already counted in Phase III osteoarthritis and neuropathic pain studies.

A.3.2 Cost Through NDA

Year	Cost
1999	29.9
2000	93.2
2001	50.5
Total Cost	173.6

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Development Plan
ABT-594

8

A.3.3 Development Milestones

The project milestones for ABT-594 are as follows:

Milestones	Date
PPCC Approval	12/96
Start Funding	1/97
Go/No Go Preclinical Safety	6/97
Start Phase I Europe	7/97
File IND (Liquid)	2/98
Start Phase II U.S.	7/98
Go/No Go Clinical Efficacy	9/99
File CTX/CTN	10/99
End of Phase II Mtg. w/FDA	11/99
Start Phase III U.S./Europe	12/99
Start Phase I Japan	2/00
Start Phase III Bridging Japan	1/01
File Europe - EMEA	12/01
File U.S. NDA - FDA	12/01
File Japan - Koseisho	6/02
Regulatory Approval U.S.	6/03

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DEVELOPMENT PLAN

June, 1999

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6668-R2

Analgesia Venture (6/23/99)
Development Plan
ABT-594

Table of Contents

	Page
A. Background and Rationale	1
A.1 Drug Class and Pharmacological Characteristics	1
A.2 The Disease Class	1
A.3 Pathophysiology and Treatment Options	2
B. Commercial	8
B.1 Market Overview	8
B.2 Pipeline	12
B.3 Unmet Needs	14
B.4 ABT-594 Target Product Profile	15
B.5 Forecast	16
C. Major Challenges and Strategies	19
C.1 Project History	19
C.2 Registration	20
C.2.1 Indication	20
C.2.2 Clinical/NPD	22
C.2.3 CMC	22
C.2.4 Toxicology	22
C.2.5 Discovery	22
C.3 Price Setting and Reimbursement	22
C.4 Commercial Issues and Opportunities	23
C.5 Patent Issues	24
D. Clinical Trial Program	26
D.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies	26
D.2 Registration Trials	27

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6668-R2

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ABBT 0019001

Analgesia Venture (6/23/99)
Development Plan
ABT-594

ii

Table of Contents (Continued)

	Page
D.3 Trials Aimed at Enhancing Pricing and Reimbursement	32
D.4 Trials Aimed at Facilitating Launch and Market Penetration ...	32
E. Chemistry, Formulations, Manufacturing	34
E.1 CAPD	34
E.2 PARD	36
E.3 Manufacturing	37
F. Non-Clinical	38
F.1 Toxicology	38
F.2 Metabolism	39
F.3 Animal Pharmacology	40
G. Development Cost and Sensitivity Analysis	41
G.1 --Base Case Scenario	41
G.2 Downside Scenario (Funding Decrease)	43
G.3 Upside Scenario (Funding Increase)	44

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6668-R2

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ABBT 0019002

Analgesia Venture (6/23/99)
Development Plan
ABT-594

iii

Table of Contents (Continued)

Page

List of Tables

Table 1.	Prevalence of Pain by Diagnosis1	4
Table 2.	1998 Prescription Pain Market, Rx by Analgesic Class	9
Table 3.	1998 Prescription Pain Market, Sales by Analgesic Class	9
Table 4.	Analgesia Pipeline – Key Novel Agents	12
Table 5.	Development Pipeline – Nicotinic Mechanisms	12
Table 6.	ABT-594 Target Profile	15
Table 7.	U.S. Forecast (Date of Forecast: 6/98)	16
Table 8.	Ex-U.S. Forecast (Date of Forecast: 6/98)	17
Table 9.	Global Forecast	18
Table 10.	Ongoing and Proposed Phase II, III and IIIb Clinical Studies	26
Table 11.	Summary of Planned Phase I Clinical Studies	28
Table 12.	Summary of Ongoing and Completed Phase II Studies	30

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ABBT 0019003

Analgesia Venture (6/23/99)
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ABT-594

1

A. BACKGROUND AND RATIONALE

A.1 Drug Class and Pharmacological Characteristics

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 is anticipated to be effective for the treatment of both acute and neuropathic pain. The preclinical side-effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective cholinergic channel modulator (ChCM) with high oral bioavailability in rat, dog, and monkey.

ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous systems to modulate pain perception. *In vitro* and *in vivo* studies show that the antinociceptive actions of ABT-594 are blocked by nicotinic acetylcholine receptor (nAChR) antagonists, but not by opioid receptor antagonists supporting a mechanism of action that involves nAChR modulation.

ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes. ABT-594 also selectively prevents the activation of dorsal horn neuron responses to noxious mechanical and thermal stimuli, without having effects on non-noxious mechanical and thermal stimuli that could impair sensory perception.

A.2 The Disease Class

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. The economic burden of pain in the United States is estimated at \$100 billion a year in direct and indirect costs. Approximately

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ABBT 0019004

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Development Plan
ABT-594

2

95 MM Americans per year receive drug therapy for pain, which represents about 50% of those who suffer from pain. Despite its prevalence, pain is often inadequately managed. There have been few major advances in pain therapy over the last several decades, and pain management continues to rely on nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids and certain adjuvant analgesics.

In the last five to ten years, advances in neurobiology and the development of more sophisticated animal models of clinical pain have led to a paradigm shift in the understanding of pain mechanisms. Not all pain states are the same, and different mechanisms may contribute to pain caused by non-injurious stimuli (acute nociceptive pain), by tissue injury (inflammatory pain) and by nerve injury (neuropathic pain). Tissue and nerve injury induce changes in pain pathways in the nervous system, resulting in altered processing of noxious and non-noxious sensory information, and reveal molecular targets which may not be involved in the processing of sensory information from healthy tissue.

A.3 Pathophysiology and Treatment Options

The normal response to a brief noxious stimulus, producing negligible tissue injury, serves to warn and protect the individual from potential injury. This is the "ouch" type of pain evoked by briefly touching a hot surface, or by a pin prick. Pain is perceived when the high-intensity noxious stimulus (e.g., heat or a pin prick) activates C and Aδ primary afferent nociceptive nerve fibers. The resulting impulse from the periphery reaches the dorsal horn of the spinal cord, where it is processed and transmitted to the brain. Efferent, descending pathways can also modulate the afferent impulse at the dorsal horn, probably via monoamine dependent mechanisms. Low intensity stimuli, like touch, which are transduced along Aβ fibers, are not perceived as painful in the absence of tissue injury.

In the setting of trauma, infection, surgery, burns or inflammatory diseases, a diverse range of inflammatory mediators (e.g., cytokines, kinins, prostaglandins) are synthesized and released at the site of tissue injury and inflammation, and they activate and sensitize local nociceptors (nociceptive pain). The sensitized nociceptors become spontaneously

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ABBT 0019005

Analgesia Venture (6/23/99)
Development Plan
ABT-594

3

active, they respond in an exaggerated fashion to normally mildly painful stimuli (hyperalgesia), and they can then be activated by normally non-noxious stimuli such as light touch (allodynia). This phenomenon, known as peripheral sensitization, is thought to account for primary hyperalgesia, e.g., increased pain and tenderness at the site of injury.

The ongoing barrage of C-fiber impulses arriving from the sensitized periphery also triggers hyperexcitability of neurons in the spinal cord (central sensitization) and contributes further to allodynia and hyperalgesia.

Osteoarthritis pain results from activation of pain fibers in the periosteum, at the insertion point of tendons and synovia, from pressure within the joint and, to a minor extent, inflammatory pain in and around the joint. Although not well recognized, osteoarthritis pain (like any chronic painful condition) is probably associated with peripheral and central sensitization.

Neuropathic pain results from injury to the central or peripheral nervous system due to a variety of causes including trauma, surgery, disease, and certain drugs. Following nerve injury, a number of changes occur in the periphery which contribute to abnormal painful sensations. The damaged nerve may begin to discharge spontaneously at atypical (ectopic) locations, including the neuroma and demyelinated zones at the site of nerve injury, and the associated dorsal root ganglion (DRG). These ectopic discharges produce spontaneous burning pain. In addition, the increased barrage of impulses from the periphery leads to hyperexcitability of spinal cord dorsal horn neurons (central sensitization), resulting in hyperalgesia and allodynia.

Inflammatory and neuropathic pain can co-exist. For example, a cancer patient may experience inflammatory pain following surgery or due to inflammation and tissue damage at the site of the tumor, and neuropathic pain due to radiation or chemotherapy induced neuropathies, or due to tumor encroachment on the peripheral nervous system.

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Development Plan
ABT-594

4

Table 1. Prevalence of Pain by Diagnosis¹

Diagnosis	Prevalence (MM)	
	U.S.	Worldwide ²
Musculoskeletal Pain	56	160
Post-Operative Pain	30	83
Neuropathy (Diabetic, PHN, etc.) Pain	28	75
Osteo/Rheumatoid Arthritis Pain	17	46
Cancer Pain	2	5
Total Pain Diagnoses	133	359

1. Decision Resources, 1996. Data reflect number of pain diagnoses such that a patient might be diagnosed with two pain diagnoses of different pain types at separate visits.
2. Germany, France, Italy, Spain and Japan.

Prescription analgesics for pain other than headache can be broken down into three major categories: opioids, non-opioids, and adjuvant analgesics.

Opioids analgesics such as morphine and codeine, are generally used for the treatment of moderate to severe pain and are often added when pain is inadequately controlled by acetaminophen and/or NSAIDS. Opioid analgesics are used primarily for the pain associated with surgery, injuries, musculoskeletal disorders, and cancer pain. Opioids are considered the drug-of-choice for severe acute pain and cancer pain. Although highly efficacious, opioids are associated with a significant number of side effect liabilities. Constipation is the most common adverse event associated with opioid therapy, and prophylactic laxatives are widely prescribed with opioids. Nausea and vomiting, sedation and cognitive impairment are also often encountered. Respiratory depression, while less frequent, is the most dangerous side effect of opioid therapy. In addition to the fear of respiratory depression, concerns about addiction, tolerance, use diversion and the fear of regulatory action ("opiophobia") have all proven to be significant impediments to the use of opioids. Opioids are generally not prescribed for chronic non-malignant pain conditions due to patient tolerance and the potential for addiction. Opioids are scheduled compounds that are subject to Drug Enforcement Agency (DEA) regulations, impacting

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ABBT 0019007

Analgesia Venture (6/23/99)
Development Plan
ABT-594

5

prescribing and product distribution. The extent of the regulations are based on the abuse potential of each product; the higher the abuse potential, the more restrictive the control over distribution.

Opioid analgesics can be divided into opioid and opioid-combination agents. Opioids are either derivatives of opium or synthetic agents with opium-like properties. Opioids produce analgesia by binding to various opioid receptors, which in turn decrease pain perception within the central nervous system but do not affect the source of pain or reduce inflammation. Opioid-combination agents combine an opioid agent with another analgesic such as aspirin or acetaminophen. The advantage of this type of combination agent lies in its broad pain coverage. The aspirin or acetaminophen acts on the peripheral nervous system while the opioid decreases the degree of pain experienced by the central nervous system.

Non-opioid analgesics are used for the management of mild to moderate pain and as an adjunct to the opioids in the management of moderate to severe pain. They are generally used in chronic pain syndromes and when pain severity is mild to moderate. Non-opioid agents can be divided into non-steroidal anti-inflammatory drugs (NSAIDs) and other non-opioids. Prescription NSAIDs are used to treat osteoarthritis, rheumatoid arthritis, lower back pain, and other chronic pain conditions in addition to some mild to moderate acute pain conditions. NSAIDs inhibit the synthesis of prostaglandins, substances released by the body after trauma and which are responsible for inflammation, increased body temperature and the sensitization of pain receptors. NSAIDs generally have fewer CNS side effects than do opioid agents. However, NSAIDs may cause potentially serious GI side effects including gastric ulceration and bleeding. COX-2 agents may cause fewer GI side effects, but do not improve upon the analgesic efficacy of NSAIDs.

Currently, NSAIDs are the primary treatment for pain associated with osteoarthritis. Recently approved COX-2 inhibitor agents are likely to make significant incursions into the NSAID market especially in the elderly patient population on chronic therapy at risk for GI bleed. The NSAIDs and acetaminophen are associated with a "ceiling effect" for their analgesia, i.e. complete pain relief cannot be achieved, even after dose escalation, which significantly limits their utility to treat severe pain. Acetaminophen has analgesic

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ABT 0019008

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Development Plan
ABT-594

6

and antipyretic activity, but lacks anti-inflammatory activity. The mechanism of action of acetaminophen is poorly defined, but appears to involve effects in the CNS. Acetaminophen has no effects on platelet function and no gastrointestinal toxicity, but may be hepatotoxic particularly in heavy drinkers and patients with chronic liver disease.

Other non-opioid analgesics include Ultram (tramadol HCl), which was approved in the U.S. in 1995 after more than 15 years of use in Europe. Tramadol is an analgesic that has an indication for the treatment of moderate to moderately-severe pain. The product has a unique dual mechanism of action via opioid and non-opioid mechanisms, and is not currently scheduled. Tramadol may, however, reinitiate physical dependence in previously opioid-dependent patients. It is recommended that tramadol not be used in opioid-dependent patients, in patients with a tendency to abuse drugs, or in patients chronically using other opioids. In addition, tramadol is under postmarketing surveillance for abuse potential, and may eventually receive scheduling status.

Adjuvant analgesics are drugs that are used for pain relief, but also have other significant indications (antiepileptic, antidepressant). The analgesic adjuvants include a number of compounds which have primary indications other than pain control, but have been found by clinical experimentation to have analgesic activity in certain types of pain. The onset of pain relief with adjuvant agents is frequently delayed due to the need for dose titration to minimize toxicities and for adaptive mechanisms to be induced. In addition, adjuvant agents are associated with significant toxicities. These drugs are most commonly used to treat the many types of neuropathic pain but have modest efficacy. A significant number of neuropathic pain patients, however, are treated with NSAIDs, muscle relaxants and non-opioid analgesics, despite their ineffectiveness. Opioids may be effective in neuropathic pain but are generally avoided because of abuse liability. The most common drug classes used as adjuvants are tricyclic antidepressants and antiepileptic drugs, which tend to have fairly significant side effect profiles. The only drug with a specific indication for any type of neuropathic disorder is Tegretol (carbamazepine) for trigeminal neuralgia. Generally, the use of adjuvant analgesics to treat neuropathic pain is based on trial and error using sequential drug trials.

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ABBT 0019009

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Development Plan
ABT-594

7

Gabapentin has a significant portion of its sales as off-label use in the treatment of neuropathic pain. Gabapentin, an anti-epileptic agent, has been used in neuropathic pain largely based upon trial and error. More recently, two placebo-controlled, double blind randomized trials demonstrated gabapentin's efficacy in pain associated with diabetic peripheral neuropathy (a type of distal symmetric neuropathy) and in post-herpetic neuralgia. While gabapentin's effect is modest, its success is largely attributable to the large unmet need in neuropathic pain and to the paucity of adverse events associated with gabapentin.

Recent findings in the understanding of pain mechanisms have led to a new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the $\alpha 2\delta$ calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability. A significant unmet need exists in the pain management market for products that are safer, non-abusable, non-addicting, non-scheduled, non-tolerance producing, and efficacious in oral and parenteral forms for the treatment of moderate to severe pain, especially for chronic nociceptive and neuropathic pain.

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Development Plan
ABT-594

8

B. COMMERCIAL

B.1 Market Overview

Pain is the most common symptom for which individuals seek medical assistance. Pain is the primary complaint of 50% of all patients who visit a physician. In 1996, the worldwide diagnosed pain population was 427 million, of whom 37% were from the U.S. and 63% from outside the U.S. Physician or patient concern about drug safety and side effect profiles, fear of addiction, the use of OTC therapies, or non-pharmacological treatments account for the 30-50% of patients who seek treatment for pain but are not prescribed an analgesic. Chronic pain sufferers may account for as much as 10-20% of the adult population, one-fourth to one-half of which obtains inadequate pain relief.

Pain is categorized by duration (acute or chronic) and by severity into one of three segments: mild, moderate, and severe. The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen, ibuprofen and other NSAIDs. The moderate and severe segments of the market have many opioid product offerings that are mostly generic, undifferentiated and inexpensive. Many patients, however, develop tolerance to these drugs, and opioids are scheduled products that create administrative burdens and barriers to prescribing. These barriers are particularly high in European markets. As a result, opioid use is restricted almost entirely to cancer pain, and there exists a large unmet need for effective treatment of severe pain. Prescription NSAIDs are generally written for chronic pain of moderate severity, though potentially serious GI or renal side effects may complicate treatment.

Total U.S. sales of prescription pain medications reached over \$5.1 billion in 1998. While opioids and combination opioids accounted for the majority of analgesic prescriptions at 55%, NSAIDs had the highest share of total prescription analgesic sales at 37%.

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

9

The prescription pain market is made up of three classes of analgesics; opioids (and combination products), NSAIDs and other non-opioids (including aspirin and acetaminophen). Anesthetics, anti-migraine and adjuvant analgesics are not included in this market definition. The following tables show U.S. and ex-U.S. prescription and sales volume by class for 1998.

Table 2. 1998 Prescription Pain Market, Rx by Analgesic Class

Class	1998 U.S. TRx (M)	U.S. TRx CAGR '95-'98	1998 ex-U.S. TRx (M)	ex-U.S. TRx CAGR '95-'98
Opioids	143,843	6.2%	N/A	N/A
NSAIDs	79,928	(2.5%)	N/A	N/A
Other Non-Opioids	37,463	7.5%	N/A	N/A
TOTAL	261,234	3.5%	N/A	N/A

Source: IMS

Table 3. 1998 Prescription Pain Market, Sales by Analgesic Class

Class	1998 U.S. Sales (\$MM)	U.S. Sales CAGR '95-'98	1998 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '95-'98
Opioids	\$1,905	16.3%	\$682	14.8%
NSAIDs	\$1,926	(1.1%)	\$3,978	(2.5%)
Other Non-Opioids	\$1,328	(5.4%)	\$1,391	1.7%
TOTAL	\$5,159	3.0%	\$6,050	(0.1%)

Source: IMS; Ex-U.S. data includes retail pharmacy data from all audited markets and hospital data from major European markets and Canada only.

In the U.S., opioid analgesics are considered the drugs-of-choice for acute pain, especially of moderately-severe to severe intensity. Opioids are generally not prescribed for chronic pain conditions due to patient tolerance and the potential for addiction,

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Development Plan
ABT-594

10

although opioids are the most commonly prescribed medication for moderate to severe cancer pain. Ex-U.S. opioid use varies considerably from one country to another. The UK, France and Japan are more advanced than other ex-U.S. countries regarding their perspective on safe opioid use, and prescriptions have increased considerably over the past 5 years. In Italy, Spain and Germany, opioid use is extremely restricted, requiring patient identity cards and special prescription forms that must be obtained, in person, by the physician. Strong opioids such as morphine are often considered last resort. In both the U.S. and ex-U.S., opioids are government-scheduled products with restricted prescribing and product distribution.

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally used in chronic pain syndromes and when pain severity is of mild to moderate intensity. NSAIDs exhibit analgesic and mild anti-inflammatory properties, and thus are drugs-of-choice in such pain conditions as osteoarthritis, rheumatoid arthritis and lower back pain. NSAIDs have fewer side effects than do opioid agents, especially CNS effects. However, the products can cause potentially serious renal and gastrointestinal side effects including gastric ulceration and bleeding.

"Other non-opioids" are defined as (1) non-opioid/non-NSAID agents like aspirin, acetaminophen or tramadol, or (2) NSAIDs that are positioned and marketed as analgesics, such as ketorolac or bromfenac sodium. Other non-opioids are generally used in place of opioids to treat moderate pain, or in some cases, moderately-severe pain.

Osteoarthritis (OA) is one of the largest segments of the analgesia market, and one of the most common conditions treated by primary care physicians. Over 35 million people worldwide suffer from OA, and three-fourths of OA sufferers surveyed indicate that the disease interferes with daily activities. Estimates of worldwide sales of prescription analgesics to treat OA range from \$2.25-3 billion. According to a recent study, as many as 47% of Americans diagnosed with OA take a prescription analgesic at least occasionally for the condition. NSAIDs and acetaminophen are the standard treatments for OA. However, the new COX-2 inhibitors are expected to grow the OA market due to their expected higher levels of GI safety. This added safety would attract patients who were administered prescription or OTC NSAIDs only occasionally to avoid potentially

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Development Plan
ABT-594

11

severe gastric ulcerations and bleeding. The COX-2 inhibitors will also take share from branded and multisource prescription NSAIDs. As a result, the COX-2 inhibitors are expected to grow the OA market in prescriptions and sales, maybe by a significant amount.

Neuropathic pain is a very large, yet largely untapped market. Estimates vary widely for the number of worldwide sufferers, from as low as 20 million to as high as 50 million or more. The number of actual cases is difficult to estimate since neuropathic pain is difficult to diagnose, and is often misdiagnosed. Neuropathic pain is often treated with adjuvant analgesics such as tricyclic antidepressants, anticonvulsants and alpha adrenergic agonists. Prescription drug sales for the treatment of neuropathic pain exceed \$1 billion worldwide. In the U.S. alone, approximately \$250 million of the sales of the anticonvulsant Neurontin (gabapentin) are off label uses attributed to the treatment of neuropathic pain. However, a significant unmet need exists in the treatment of neuropathic pain since few medications provide complete pain relief and most adjuvant medications have significant side effects that preclude their long-term use. As more effective and tolerable medications become available, the neuropathic pain market is expected to experience significant growth.

Most analgesics are indicated for the treatment of one or more specific pain states. However, depending on its characteristics, a significant amount of a product's prescriptions may come from non-indicated pain states (i.e., spillover prescriptions). Therefore, a product indicated for OA is likely to be prescribed for chronic lower back pain, rheumatoid arthritis, and other pain states with similar clinical characteristics or etiologies.

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Development Plan
ABT-594

12

B.2 Pipeline

Table 4. Analgesia Pipeline – Key Novel Agents

Product	Company	Mechanism	Phase	Comment
pregabalin	Parke-Davis	Ca channel blocker	III	Neuropathic pain, chronic pain Follow-up to Neurontin
JTE 522	Japan Tobacco/J&J	COX-2 inhibitor	II	J&J has rights outside Japan
4030W92	Glaxo	Na channel blocker	II	Acute and chronic pain
vedacilidine	Lilly	muscarinic agonist	II	General pain MOA losing favor; active program?
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain MOA losing favor; active program?
GP13269	Metabasis (Gensia)	adenosine kinase inhibitor	II	General pain, epilepsy
ZD4952	Zeneca	prostaglandin receptor antagonist	II	Moderate to severe pain
GV196771	Glaxo	glycine antagonist	II	Chronic pain

Sources: ADIS, IMS, company reports

Table 5. Development Pipeline – Nicotinic Mechanisms

Product	Company	Phase	Comment
GTS-21	Taiho	II	Target is Alzheimer's Disease May have preclinical pain program
SIB-1508Y	Sibia	II	Target is Parkinson's Disease Preclinical for dementia
SIB-1553A	Sibia	II	Target is Alzheimer's Disease
CMI 980	Cytomed	Preclinical	Target is pain Epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain
RJR 2557	Targacept (RJR)	Preclinical	Target is pain. Also for cognitive defects
Nicotinic agonists	Neurosearch	Preclinical	Target is pain

Sources: ADIS, IMS, company reports

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Development Plan
ABT-594

13

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for other non-analgesic indications. The majority of the analgesic compounds in the pipeline represent incremental improvements to the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development are novel mechanisms with unique mechanisms of action. These novel mechanisms are expected to provide the bulk of the competition for ABT-594.

Among the novel agents in development, the greatest threat to ABT-594 is likely to be posed by other nicotinic compounds in development for pain. ABT-594, now in late Phase II trials, is likely probably the most advanced nicotinic compound in the analgesia pipeline. ABT-259, on the other hand, has a less substantial lead on other nicotinic compounds in development for pain. The first nicotinic compounds to be launched in the class may be for Alzheimer's Disease or Parkinson's Disease. These compounds do not represent a threat to ABT-594, unless significant safety concerns or evidence of tolerance, dependence or abuse are an issue and become associated with the class as a whole.

For the treatment of osteoarthritis (OA), the COX-2 inhibitors represent the most significant competition. The launch of Searle's Celebrex (celecoxib) in January 1999 is one of the most successful product launches in industry history. After ten weeks on the market, prescriptions for Celebrex represented 24% of new NSAID prescriptions. Merck's Vioxx (rofecoxib), approved in May 1999 is also expected to be a very successful product in the treatment of OA as well as other pain states.

The pipeline for the treatment of neuropathic pain does not have a blockbuster compound on the order of the COX-2 inhibitors. However, the follow-up to Parke-Davis' Neurontin (gabapentin) is expected to perform well. This compound, pregabalin, is significantly more potent than gabapentin which is expected to increase its efficacy while maintaining a relatively benign side effect profile.

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Development Plan
ABT-594

14

B.3 Unmet Needs

Unmet Need	Pipeline Impact
<ul style="list-style-type: none"> Efficacy in moderate to severe pain without tolerance, dependence or abuse 	<ul style="list-style-type: none"> Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities
<ul style="list-style-type: none"> Reduction in the GI adverse events profile of NSAIDs 	<ul style="list-style-type: none"> COX-2 inhibitors appear to reduce the incidence and severity of GI adverse events, but Celebrex retains labeled warnings regarding ulceration comparable to traditional NSAIDs COX-2s still demonstrate AEs at high dosage levels (small therapeutic window)
<ul style="list-style-type: none"> Overcome ceiling effect of NSAIDs 	<ul style="list-style-type: none"> More selective COX-2s (~1000 times more selective for COX-2 vs. COX-1) may allow higher dosing without incurring GI adverse events, thus overcoming current therapeutic ceiling Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594
<ul style="list-style-type: none"> Efficacy in neuropathic pain 	<ul style="list-style-type: none"> Pregabalin is expected to provide more significant relief of some types of neuropathic pain with fewer side effects than other adjuvant analgesics Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models
<ul style="list-style-type: none"> Few long-acting agents available for the treatment of acute pain 	<ul style="list-style-type: none"> Novel analgesics may have a longer duration of action than opioids

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance producing, non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe pain.

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ABT-594

15

B.4 ABT-594 Target Product Profile

Table 6. ABT-594 Target Profile

PPCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Indicated for the treatment of pain (general pain claim)	Indicated for the treatment of osteoarthritis pain	"General pain" claim not achievable due to slow onset of action; proof of principle established in molar extraction study	Medium	9/99, 1Q01	High
Effective in neuropathic pain	Indicated for the treatment of neuropathic pain	Indication specific claims now favored since general pain claim not achievable	Low	9/99, 2Q01	Medium
Effective for moderate to moderately-severe pain	N/A	No longer applicable without general pain claim	N/A	N/A	N/A
Not scheduled	No change	N/A	High	4Q02	High
Improved safety profile compared to opioids including: - less GI motility impairment - less respiratory depression - low tolerance potential - no dependence/withdrawal	No clinically significant tolerance, dependence or withdrawal	Simplify profile to focus on the most commercially important AEs	Medium	2Q01	High
	Very few abnormal LFTs	Abnormal LFTs in a few Phase I subjects	High	9/99	High
	Very low nausea/vomiting at effective dose	Relatively high incidence of nausea/vomiting in single dose Phase I & II subjects (food and dose dependent)	Medium	9/99	High
	Other safety OK	Simplify profile	Medium	9/99, 2Q01	High
	No significant or sustained differential efficacy in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	Low	9/99, 2Q01	High
	No significant or sustained differential side effect profile in nicotine users vs. non-nicotine users	Lower incidence of AEs in nicotine users in Phase II trial	High	9/99, 2Q01	Medium
	No re-initiation of cravings in ex-nicotine users	Possible due to nicotinic mechanism	Medium	2Q01	High

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Development Plan
ABT-594

16

Table 6. ABT-594 Target Profile (Continued)

PPCC/DDC Profile (12/10/97)	Current Profile (6/99)	Rationale for Profile Change	Probability	Status	Share Impact
Onset of action in less than 30 minutes	Onset of action comparable to other therapies used to treat OA	Onset of action estimated at 90 minutes in Phase II trial	Low	9/99	Medium
	Onset of action comparable to other therapies used to treat neuropathic pain	Onset of action estimated at 90 minutes in Phase II trial	High	9/99	Medium
BID/TID dosing	BID dosing	Competitive dynamics highlight importance of dosing convenience	High	9/99	Medium
No major drug interactions, especially with drugs used for common chronic conditions	No change	N/A	High	4Q00	Medium

B.5 Forecast

Table 7. U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rx's (MM)	280	285	291	297	303
- % chg	2%	2%	2%	2%	2%
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rx's (MM)	2.8	7.1	11.1	13.3	15.1
Price/Rx (\$)	34.97	35.67	36.39	37.12	37.86
Abbott Sales (\$MM)	125	254	402	495	573
R&D (\$MM)	5	5	4	4	3
SG&A (\$MM)	66	98	90	85	84
SMM (%)	97.2	97.3	97.3	97.4	97.4
Div. Margin (\$MM)	59	162	324	427	509

10 year pre-tax NPV @ 12.5% = \$1.016 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$587 MM

10 year post-tax ENVY @ 12.5% = TBD

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Development Plan
ABT-594

17

Key assumptions:

- Assumes 12/97 PPCC profile
- NDA Filed 12/01, Launch 6/03
- First in class ChCM
- Usage = 70% chronic and 30% acute
- Weighted average days per Rx = 15.6
- Stocking at 12% of first year's sales
- Detailing includes 30% of IMs, 25% of FPs and GPs, 25% of Rheumatologists, and 10% of Neurologists
- Sampling at 80% of details at launch, 8 units per detail, 5 days of therapy per unit
- Patent expires 12/2016

Forecast Update Plan:

Forecast will be updated in late June/early July 1999 to account for revised indications of OA and/or neuropathic pain and the associated spillover use in other pain states.
Forecast will be available well in advance of ABT-594 Go/No Go decision in 9/99.

Table 8. Ex-U.S. Forecast (Date of Forecast: 6/98)

	2003	2004	2005	2006	2007
Market Rx (MM)	-	-	-	-	-
- % chg					
Abbott Share (%)	1%	2.5%	3.8%	4.5%	5.0%
Abbott Rx (MM)	-	-	-	-	-
Price/Rx (\$)	-	-	-	-	-
Abbott Sales (\$MM)	60	150	250	300	320
R&D (\$MM)	3.4	3.2	2.8	2.4	2.0
SG&A (\$MM)	27	53	50	48	45
SMM (%)	95%	95%	95%	95%	95%
Div. Margin (\$MM)	26	85	182	235	251

10 year pre-tax NPV @ 12.5% = \$428

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$253

10 year post-tax ENVY @ 12.5% = TBD

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Development Plan
ABT-594

18

Key assumptions:

- First in class ChCM
- Indicated for treatment of moderate to moderately-severe pain
- Effective in neuropathic pain
- Good tolerability and safety profile
- No nicotinic effects
- Launched in all AI regions, including Japan, simultaneously (2003)

Forecast Update Plan:

- Forecast will be updated 9/99 (in time for the Go/No Go decision) to reflect results of marketing research to be conducted 3Q 1999 regarding expected uptake of 594 in OA and neuropathic pain markets, as well as potential spill-over prescribing for other pain states.

Table 9. Global Forecast

	2003	2004	2005	2006	2007
U.S. Sales (\$MM)	125	254	402	495	573
Ex-U.S. Sales (\$MM)	60	150	250	300	320
Total Sales (\$MM)	185	404	652	795	893
Total Division Margin (\$MM)	85	247	506	662	760

10 year pre-tax NPV @ 12.5% = \$1.44 B

10 year pre-tax ENVY @ 12.5% = TBD

10 year post-tax NPV @ 12.5% = \$840 MM

10 year post-tax ENVY @ 12.5% = TBD

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Development Plan
ABT-594

19

C. MAJOR CHALLENGES AND STRATEGIES

C.1 Project History

Key Milestones	
Milestone	Date
PPCC Approval	12/96
Start Phase I	7/97
Start Phase II	7/98
First Phase II Result	12/98
GO/NO GO Efficacy*	9/99
Start Phase III	1/00
Regulatory Filings (US/EU)	12/01
Regulatory Approval	6/03

* Based on Phase II studies in molar extraction, osteoarthritis, and neuropathic pain.

- At PPCC, indications considered for ABT-594 were acute vs. chronic pain, with an acute pain claim being considered to have a shorter development course, as long term toxicology studies could theoretically be avoided with this approach.
- Input from FDA (3/98) indicated that if an oral dosage form was being pursued, i.e., the drug *could* be used long term (independent of indication being sought), then long term toxicology studies would be required.
- Decision analysis review of the program (3/98 - 7/98) arrived at several conclusions:
 - A general pain indication was preferred over filing for an acute indication earlier.
 - Carcinogenicity studies should be initiated prior to first Phase II results.
 - Development of follow-on compounds (in the same cholinergic channel modulator class and in different pharmacologic classes).

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Development Plan
ABT-594

20

- Data from the first Phase II study (single dose molar extraction) indicated that ABT-594's onset of action is 1.5 - 2 hours post dose. Because a general pain indication requires efficacy in acute pain states (with more rapid onset of action), ABT-594 was considered to be unlikely to achieve a general indication. The current clinical plan targets disease-specific indications.

The global target indications for ABT-594 are for the treatment of pain associated with osteoarthritis and for the treatment of neuropathic pain.

C.2 Registration

C.2.1 Indication

A major challenge to the development of ABT-594 is the identification of an optimal indication for this novel pharmacology. An understanding of the issues regarding indications for pain management requires a definition of terms.

Disease-specific Indication: The product would be indicated for pain management associated with specific disease or condition(s) such as osteoarthritis, diabetic neuropathy or dysmenorrhea.

General Indication: The product would be indicated for use in unspecified pain states (for the management of pain) without a limit on treatment duration.

Acute Indication: The product would be indicated for use in unspecified pain states, with duration of use of at most 5 days (typically, post-operative pain).

Historically at FDA, a typical submission has included approximately six efficacy studies (several single-dose dental pain studies, and several multiple dose orthopedic or post-operative pain studies) and safety studies. This package has resulted in a general pain indication.

While the FDA has regarded this approach as satisfactory given the broad analgesic efficacy of older compounds (NSAID's and opioids), newer pharmacologic approaches have created concerns at FDA that a drug studied for short periods may not be effective

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McCarthy Deposition Exhibit 6

P's Exhibit BV

Part 2

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Development Plan
ABT-594

21

in chronic pain states (e.g., low back pain, neuropathic pain). An FDA Advisory Committee meeting (March, 1998) recommended that acute studies should support *only* an acute indication, and chronic studies (in addition to acute studies) are required to support a general indication. The FDA indicated that it may use labels that distinguish compounds with efficacy in neuropathic pain from those without efficacy in this mechanistically distinct pain type. Currently no regulatory guidelines exist (FDA or EMEA) as to the requirements for a neuropathic pain indication. Carbamazepine (Tegretol, Novartis) is indicated for the management of trigeminal neuralgia, and topical lidocaine (Lidoderm, Endo) is indicated for the management of post-herpetic neuralgia.

Recent FDA/CPMP guidelines exist regarding disease-specific indications for osteoarthritis and rheumatoid arthritis and two COX-2 inhibitors have recently been approved by the FDA. Celebrex (celecoxib, Searle) is approved for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis. Vioxx (rofecoxib, Merck) is approved for the relief of signs and symptoms of osteoarthritis, dysmenorrhea (painful menstruation) and acute pain. A CPMP guideline recommends 6 month studies (vs. 3 months studies required by FDA) to support arthritis indications. For the EU there exists no precedent for a compound approved through the EMEA central filing procedure for a pain claim. Meetings to review our clinical trial strategy with worldwide regulatory authorities are planned to be scheduled after the GO/NO GO decision (9/1999).

Marketing research is ongoing to assess the commercial viability of the target indications: the treatment of pain associated with osteoarthritis and the treatment of neuropathic pain.

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Development Plan
ABT-594

22

C.2.2 Clinical/NPD

- Issue:** If ABT-594 is scheduled, the NPV is significantly reduced.
- Strategy:** An expert advisory meeting took place 11/98. The advisors felt it was unlikely that ABT-594 would be scheduled and recommended that we conduct several preclinical/clinical studies on the compound identified for Phase III development after the GO/NO GO (9/1999).

C.2.3 CMC

- Issue:** We are at risk for possible increases in the cost of drug substance because we are dependent on other vendors to manufacture ABT-594 drug substance.
- Strategy:** Abbott cannot manufacture highly potent compounds. CAPD has selected Chemsyn as the manufacturer of the bulk drug substance.

C.2.4 Toxicology

- Issue:** Six month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long term toxicology studies.
- Strategy:** No adenomas have been found in the study. Early deaths in the 2 year carcinogenicity study will be closely monitored. No further studies are recommended at this time.

C.2.5 Discovery

- Issue:** Given our leadership position in cholinergic channel modulator pharmacology, a critical program challenge is the establishment of milestones that optimize timing and decision-making for clinical development of follow-on compounds.
- Strategy:** ABT-259 was approved for Transition Team evaluation at DDC 9/98. An additional cholinergic channel modulator compound and an adenosine kinase inhibitor are currently targeted for DDC by 4Q 1999.

C.3 Price Setting and Reimbursement

Pricing trends in the U.S. market will remain relatively stable in the short term due to two factors. First, the effect of higher-priced branded products entering the market in each analgesic class is tempered by the loss of patent protection of other branded

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Development Plan
ABT-594

23

products, and the resulting price erosion due to generic competition. Secondly, the large size of the prescription pain market tends to absorb the impact of individual products' prices in each analgesic class. In the long term, however, the entry of several higher-priced novel analgesics may create an upward trend in prescription analgesic prices.

Due to the competitiveness of the pain management market, ABT-594 must favorably complete outcomes and pharmacoeconomic studies in order to gain significant formulary acceptance and use in managed care organizations (MCOs) and institutional settings. Marketing research and consultation with the PPD managed care department will help determine the appropriate number of studies, comparators and desired endpoints.

C.4 Commercial Issues and Opportunities

Issues

- ABT-594 must demonstrate an excellent safety profile for broad usage by general practitioners
 - Potential for AEs (nausea) still exists
 - Potential for addiction due to nicotinic mechanism still exists
- No DEA scheduling will be key to market success
- Implications, if any, of the differential side effects in smokers vs. non-smokers must be determined
- ABT-594 must demonstrate an advantage over COX-2s for the treatment of OA/RA pain in order to compete in this market
- Other novel analgesics (e.g., pregabalin, 2nd generation COX-2s) may beat ABT-594 to the market
- ABT-594 may face significant pricing pressures ex-US, given the large number of existing pain drugs, many of which are generic

Opportunities

- ABT-594 expected product profile would satisfy several significant unmet needs in the analgesia market
 - Avoids scheduling, addiction and tolerance issues of opioids while providing relief of moderate to severe pain

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Development Plan
ABT-594

24

- Overcomes ceiling effect of NSAIDs while offering equal or better safety profile
- Efficacious in neuropathic pain
- PPD primary market research and input from the European Pain Advisory indicate that physicians would embrace a drug with these attributes
- Although molar extraction studies indicate that ABT-594 is not appropriate for treatment of acute nociceptive pain, the total available market for ABT-594 is large
 - The osteoarthritis market is among the largest segments of the analgesia market
 - The neuropathic pain market is large and significantly underserved
 - A significant amount of "spillover prescribing" for other chronic pain states is likely
- ABT-594 is likely to be the first nicotinic acetylcholine receptor modulator, indicated for treatment of pain, to reach the market (other compounds with a nicotinic mechanism may launch before ABT-594, labeled for other indications such as Alzheimer's Disease or Parkinson's Disease)
- US market would likely support premium pricing for a novel analgesic offering advantages over currently available agents
- Potency of ABT-594 ensures low cost of goods

C.5 Patent Issues

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing generic coverage for ABT-594 and ABT-259 and a large class of structurally related analogs. The original filing date for this application dates back to October 9, 1992, and since this predates a 1996 change in patent law, we are afforded a choice of 20 years from date of filing or 17 years from date of issue, of which 17 years from issue provides the longer patent life. The anticipated expiration of patent coverage for composition of matter for ABT-594 and ABT-259 will be June, 2016. An additional application (6013.US.01), which includes species claims to ABT-594 and ABT-259 as well as use claims for the treatment of pain, was filed in December, 1996 and is pending. If this patent is allowed, it will provide 20 years from date of filing, which will extend the patent life of ABT-594 and ABT-259 to December, 2016.

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

25

The original application providing generic composition of matter coverage was filed broadly ex. U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

Issue: We may have to pay for use of proprietary technology in preclinical development.

Strategy: A meeting was held at Abbott on 2/99 with representatives from SIBIA Neuroscience. SIBIA presented both on their technology platform and two compounds that are in early Phase II (SIB 1508Y) and Phase I (SIB 1553) development. An exclusive license for SIBIA's technology platform has been granted to Lilly, 5/99.

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Development Plan
ABT-594

26

D. CLINICAL TRIAL PROGRAM

D.1 Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Given the spectrum of analgesic activity of ABT-594 in preclinical animal models of pain, the clinical development program for ABT-594 will evaluate the safety and efficacy of ABT-594 for the treatment of neuropathic pain and pain associated with osteoarthritis. In addition, pilot studies are planned to assess the safety and efficacy of ABT-594 for the treatment of pain associated with cancer.

Table 10. Ongoing and Proposed Phase II, III and IIIb Clinical Studies

Indication (Study Type)	Phase II		Phase III		Phase IIIb	
	# Studies	# Patients	# Studies	# Patients	# Studies	# Patients
Osteoarthritis						
U.S.	1 ^c	250	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Neuropathic Pain						
U.S. ^a	1 ^c	150	3 ^a	1800	-	-
Europe	-	-	1 ^a	600	-	-
Japan	-	-	1 ^b	300	-	-
Cancer Pain						
U.S.	2	500	-	-	-	-
Long-Term Safety						
U.S.	-	-	1 ^a	600 ^d	-	-
Europe	-	-	1 ^a	300 ^d	-	-
Pricing Studies						
U.S.	-	-	-	-	1	500
Europe	-	-	-	-	1	500
Canada	-	-	-	-	1	500
Australia	-	-	-	-	1	500
TOTAL	4	900	12	5400	4	2000

^a. Registration Trial

^b. Bridging Study

^c. Ongoing

^d. Patients already counted in Phase III osteoarthritis and neuropathic pain studies.

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Development Plan
ABT-594

27

D.2 Registration Trials

Phase I

Seven Phase I studies have been completed with ABT-594. These initial Phase I studies have provided a preliminary determination of the pharmacokinetic, safety and tolerability profile of single and multiple dose administration of an oral liquid formulation of ABT-594 and the comparative bioavailability and effect of food on oral liquid and solid oral soft elastic capsule (SEC) and hard gelatin capsule (HGC) formulations.

Approximately 171 subjects have received at least one dose of ABT-594 (25 µg to 200 µg) as an oral solution under fasted (i.e., after a 10-hour fast) or fed conditions (i.e., approximately 30 minutes after a meal was served).

For the ABT-594 oral solution, dosing under fasted conditions was limited by vomiting after single dose administration at doses of 100 µg or higher; however, improved gastrointestinal (GI) tolerability was generally noted with continued dosing under fasted conditions and when ABT-594 was administered under fed conditions. The most frequently observed adverse events were dizziness, nausea, and vomiting. Most adverse events were mild in severity and occurred at doses of 100 µg or higher.

The pharmacokinetics of ABT-594 were linear at doses from 25 µg to 150 µg after single and multiple dose administration. No unexpected accumulation was observed after multiple dosing. Approximately 50% of an ABT-594 dose was recovered in urine. There was no effect of food on the C_{max} and AUC of ABT-594. The occurrence of adverse events of dizziness, nausea, and vomiting was significantly correlated with C_{max} , AUC, and dose.

Two Phase I studies (Study M97-706, Study M98-984) have assessed the bioavailability of ABT-594 oral solution, SEC, and HGC formulations. In Study M97-706 (n=22), the bioavailability of a single 100 µg dose of ABT-594 25 µg and 50 µg SEC formulations was shown to be equivalent to that of an ABT-594 oral solution formulation with regard to C_{max} and AUC. In Study M98-984 (n=23), based on preliminary analysis, the bioavailability of a single 100 µg dose of a 25 µg HGC formulation was similar to that of

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ABT-594

28

a 25 µg SEC formulation. In the same study, preliminary analysis also showed the pharmacokinetics of a single 150 µg ABT-594 dose to be similar for both the SEC and HGC formulations. In these studies, a single 100 µg dose of the SEC and HGC was well-tolerated with excellent GI tolerability (i.e., nausea, vomiting) under fasted conditions. For a single 150 µg dose, less vomiting was observed with the HGC and less nausea with the SEC under fasted conditions as compared to the oral solution in previous studies.

Eighteen additional Phase I studies are planned to be included in the registration package. These Phase I studies will be conducted so that data on specific drug interactions and pharmacokinetics and safety of ABT-594 in special populations can be included in the labeling and package insert once the product is approved. A table summarizing these studies is presented below:

Table 11. Summary of Planned Phase I Clinical Studies

Study	Number of Studies	Planned Number of Subjects	Anticipated Start Date
Bioavailability	3	72	4 Q '99
Human Metabolism	1	6	3 Q '99
Drug Interaction	6	192	1 Q '00
Special Populations:			
Renal Impairment	1	32	1 Q '00
Hepatic Impairment	1	32	
Smokers	1	48	
Geriatric	1	48	
Cardiovascular Safety	1	32	1 Q '00
Japanese Population:	3		
Single Rising Dose	1	60	1 Q '00
Food Effect	1	12	1 Q '00
Multiple Rising Dose	1	60	2 Q '00
Total Planned Phase I Studies:	18	594	

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Development Plan
ABT-594

29

Phase II

Five Phase II dose-ranging studies have been initiated. Two Phase II studies in dental pain following third molar extraction surgery (M97-772 and M97-897) used an ABT-594 oral liquid formulation have been completed. Two Phase II studies, one in neuropathic pain (n=150) and one in osteoarthritis (n=250) are currently ongoing. One study in post surgical pain was initiated but prematurely terminated due to the onset of active ABT-594.

The single dose molar extraction (M97-772) demonstrated that ABT-594 has analgesic effects with no differential effectiveness based on prior nicotine use, gender or baseline pain severity. However, these analgesic effects were associated with adverse events of nausea, vomiting and dizziness and a slow onset of action (1.5-2.0 hours). As a general pain claim is supported by evidence of acute efficacy, these results suggested that a general pain indication is unlikely to be achieved for ABT-594. The molar extraction model assessed the single dose safety and efficacy, dose response and onset of effect of ABT-594, but did *not* assess the multiple dose safety, efficacy, and durability of effect of ABT-594. These parameters are being assessed in the ongoing 3 week Phase II neuropathic pain (M98-833) and osteoarthritis (M98-826) studies.

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Development Plan
ABT-594

30

The five initiated Phase II dose-ranging trials are summarized in the following table:

Table 12. Summary of Ongoing and Completed Phase II Studies

Protocol No.	Study Description	ABT-594 Doses	Treatment Duration Regimen	Target Enrollment	Patients Enrolled	Status Conclusion
M97-772	Molar Extraction	25, 50, 75, or 100 µg	1 Day; QD	288	290	Completed; Efficacy seen at 100 µg dose; Onset at approximately 2 hours.
M97-897	Molar Extraction	100 µg	1 Day; QD	45	45	Completed; Efficacy not demonstrated; 90% of ABT-594 subjects received rescue medication prior to 2 hour analgesic onset.
M98-836	Post General Surgery	25, 50, or 75 µg	1 Day; QD	250	2	Study prematurely terminated due to slow onset of action of ABT-594 in M97-772
M98-833	Neuropathic Pain	25 or 75 µg	3 Weeks; BID	150	136	Study is ongoing
M98-826	Osteoarthritis	25, 50, 75 µg	3 Weeks; BID	250	256	Study is ongoing

Two Phase II pilot studies in patients with moderate to severe cancer pain are planned for the registration package. These studies are not aimed at an indication, but will be supportive studies to help establish favorable competitive position and regulatory approval. Each study will be a randomized, double-blind, placebo-controlled, morphine-sparing study of approximately 2 doses of ABT-594 in approximately 250 cancer patients.

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Development Plan
ABT-594

31

Go/No Go Decision:

A Go/No Go decision is planned for 9/99 based on the results of ongoing Phase II studies in neuropathic pain and osteoarthritis, and market research on disease specific claims (i.e., relief of signs with symptoms of neuropathic pain, or relief of signs and symptoms of osteoarthritis).

To support a Go decision for any indication, osteoarthritis (OA) and/or neuropathic pain (NP) Phase II studies should:

1. show trends such that Phase III studies will have 80% power to detect significant improvement associated with ABT-594 vs. placebo;
2. show acceptable safety;
3. show no clinical evidence for abuse liability.

For osteoarthritis, Phase II studies should also provide evidence that adequately powered Phase III studies would not show superiority of active control (e.g. ibuprofen) compared with ABT-594.

Phase III

The Phase III program is aimed at obtaining indications for the treatment of pain associated with osteoarthritis and neuropathic pain. The Phase III program in osteoarthritis and neuropathic pain will each consist of four 600 patient Phase III studies that will be conducted in the United States and Europe, and one 300 patient bridging study that will be conducted in Japanese subjects. Although a minimum of two pivotal studies are required for registration, this plan provides some back up should a study fail to meet its primary efficacy measure to statistical significance.

Each Phase III study will be a randomized, double-blind, placebo-controlled comparative study and will evaluate two doses of ABT-594. The duration of treatment for the Phase III osteoarthritis trials will range from 3 months to 6 months. The duration of treatment for the Phase III neuropathic pain studies will be approximately 3 months. Each Phase III program will enroll approximately 2400 patients and is designed to stand alone should one indication not show sufficient efficacy.

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Development Plan
ABT-594

32

In addition to these studies, two long-term, open-label safety studies are also planned for the registration package. One study will be conducted in the United States and the other will be conducted in Europe. The purpose of these trials will be to obtain the required long-term safety data on ABT-594. These studies will allow patients who have participated in any Phase III study conducted in the United States or Europe the option of receiving ABT-594 on a long-term basis. In addition, patients who never received ABT-594 who meet the inclusion criteria will be allowed to receive ABT-594 on a long term basis.

D.3 Trials Aimed at Enhancing Pricing and Reimbursement

Phase IIIb

Late Phase IIIb studies will be devoted to comparative studies using key analgesic competitors. Phase IIIb will examine issues of pricing, market penetration and pharmacoeconomics. Four Phase IIIb pricing studies are planned to be completed prior to market launch. These studies will not be completed at the time of NDA/EMEA submission. Each study will enroll approximately 500 patients. The location (country) in which these studies will be conducted will be selected to help obtain market penetration and obtain optimum pricing on a world-wide basis. At this time, it is anticipated that one study will be conducted in each of the following four countries: Australia, Canada, United States and Europe.

Phase IV

Phase IV studies will be planned once the results of Phase III studies are obtained and will be based upon the important analgesic competitors at the time of Phase IV trials.

D.4 Trials Aimed at Facilitating Launch and Market Penetration

Price determination, reimbursement status, product positioning, and product promotion will be critical for the commercial success of ABT-594. Given the recent market entry of COX-2 inhibitors, they will likely form much of the competition at the time ABT-594 is expected to launch. Phase IIIB outcomes and reimbursement studies in the U.S. and Europe are currently planned to start in 1Q01 and 2Q01, respectively. The specific tasks listed below are proposed to establish the market value of ABT-594:

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Development Plan
ABT-594

33

Quantification of the Health and Economic Burden of Chronic Pain (3Q'99)

1. Description of Practice Pattern Variation in Major Markets (4Q'99)
2. Development of a Decision-Analytic Model (4Q'99)
3. Preparation and Execution of a Phase III Piggyback Protocol (1Q'00)
 - Health-Related Quality of Life
 - Economics
4. Development and Execution of a Naturalistic Outcomes/Cost-Effectiveness Phase IIIB Trial (1Q'01)

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Development Plan
ABT-594

34

E. CHEMISTRY, FORMULATIONS, MANUFACTURING

E.1 CAPD

Process development remains on schedule to meet the commercial cost objective. Cost of goods was originally targeted to be \$0.125/day. This was based upon a 50 mg/day dosage. It now appears a dosage projection of less than 0.1 mg/day is more likely. Based upon this dosage scenario, it is expected a bulk drug substance cost of \$0.02/day can be achieved at launch. The target cost of drug substance at launch is \$2,500/kg.

ABT-594 bulk drug substance will be manufactured only at ChemSyn Laboratories in Harrisonville, Missouri. ChemSyn has been audited by CAPD supplier quality assurance group and approved as a supplier of bulk drugs. ChemSyn has recently completed construction of a new facility for the manufacture of highly potent drugs. This new facility is where they will manufacture registration batches for ABT-594 in August of 1999. The intermediate for ABT-594, BOC azetidine alcohol (BAA), will be manufactured only at Regis Technologies in Morton Grove, IL. Regis will be manufacturing their registration batches in May and June of 1999. As time allows, the process development team will optimize the process to manufacture the bulk drug substance in 1999. The development team will also work with the analytical support groups to set specifications on materials and intermediates used in the process and define the in-process testing required for control of the manufacturing process. All pertinent impurities will be identified and standards prepared to support analytical method development for CCM.

Bulk Drug Substance Cost Status

Bulk drug substance cost is expected to be \$20,000/Kg at the time of launch. Approximately 40% of the cost reflects manual charges. The balance of the costs includes labor and equipment, process support charges and supplier profit margin.

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Development Plan
ABT-594

35

Event	Year/Source	Cost/KG	Actual/Projected
DDCC	1996 / D-45L	\$200,000	Actual
	1997- CAPD	\$175,000	Actual
	1998- SICOR	\$40,000	Actual
NDA Lots	1999- CHEMSYN	\$29,000	Projected
NDA Filing	2001	\$29,000	Projected
Validation Lots	2002	\$20,000	Projected
Launch	2003	\$20,000	Projected

The projected cost of ABT-594 bulk drug substance at launch (6/03) that was established during PPCC (12/96) was \$2,500.00/kg. The current projected cost of bulk drug substance at the time of launch is projected to be \$20,000.00/kg

The projected average daily dose is expected to be approximately 200 µg/day. Based upon a dosage projection of 0.2 mg, it is expected that the cost of drug substance at launch will be approximately \$0.004 per day.

ABT-594 Bulk Drug Substance Requirements

Project: G02Q143-010

End Q4 1999

Inventory
Balance

15 kg

	Bulk Deliveries		Usage (Quantity)			
	Description	Quantity	Clinical	Formulation	Scale-Up	Inventory
Q1 2000			0.5 kg	0.5 kg		14.0 kg
Q2 2000				0.5 kg	9.0 kg	4.5 kg
Q3 2000					3.0 kg	1.5 kg
Q4 2000						
Q1 2001						
Q2 2001						
Q3 2001						
Q4 2001	Validation Lots (n-3)	15 kg			3.0 kg	13.5 kg

Lead Time (request to delivery; weeks) 8

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Development Plan
ABT-594

36

E.2 PARD

Clinical Formulations: Rising dose safety and molar extraction studies were performed using a solution formulation. Phase II studies in osteoarthritis and neuropathic pain are underway using a softgel capsule formulation (SEC). The softgel formulation was shown to delay T_{max} , therefore, a rapidly dissolving hard gelatin capsule (HGC) formulation has been developed as the target Phase III formulation. A 25 mcg HGC is currently in a biostudy vs. SEC. A 75 mcg HGC will be tested for bioavailability 6/99.

Commercial Formulation: Primary candidate for commercial formulation is HGC at dosage strength(s) to be determined by results of Phase II studies.

Formulation-Dependent Absorption Rate: If therapeutic onset is too slow with oral solution and capsule formulations, sublingual dosing may provide more rapid absorption. To this end, clinical supplies of "Zydis" instantly disintegrating tablets have been manufactured. Rapidly disintegrating conventional tablets are also possible, avoiding royalty and manufacturing payments to Schere DDS. Biostudy with sublingual dosing is on hold.

Key Issues: Formulation and processing alternatives are limited by three factors: (1) content uniformity challenges due to low dose, (2) incompatibility with many commonly used excipients, and (3) low allowable employee exposure limits. The HGC formulas under development address factors (1) and (2). Factor (3) will require capital investment at PPD's Abbott Park or Puerto Rico manufacturing facilities, or manufacture by a third party (TPM). Preliminary evaluation of facilities modifications has been done; preliminary evaluation of TPMs has occurred as a result of other projects.

Critical Path Activities: Formulation scale-up is expected to occur 2Q00; NDA stability lots are expected to be manufactured 3Q00. 1 year stability results are expected to be available 9/01 in support of the 12/1/01 FDA/EMEA submissions.

IV Formulation: Parenteral formulation is on hold. It is expected that a lyophilized formulation will be required. Clinical supplies may be available 6 months post-funding.

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Development Plan
ABT-594

37

E.3 Manufacturing

The primary manufacturing sites in consideration are API, AP16 and RP Scherer. API Potent Drug Module would produce hard gelatin powder filled capsules. This process utilizes the 600L TK Fielder granulator, vacuum V-Blender, a potential milling step and encapsulation. AP16 Microwave Gral process would also produce hard gelatin powder filled capsules. This process involves the 300L microwave granulator, Bin blending and encapsulation. RP Scherer would produce softgel capsules. This process includes a Hicks Reactor, a vessel to reduce particle size and softgel capsulation. The granulation process demonstrated excellent stability and dissolution properties. However, both the API and AP16 options require significant capital. The RP Scherer formulation is doable but is sending the business outside. We are gathering detailed information on cost estimates for each manufacturing option. Manufacturing options are constrained by extremely low employee exposure limit (EEL) of 1 ug/m³.

Timeline for manufacturing include the following: 1) Phase III supplies starting 9/1999, 2) Identification of manufacturing site 9/1999, 3) Upgrade of Abbott site if necessary starting 9/1999, 4) Go/No-Go decision 9/1999, 5) Prescale up runs 2nd Qtr/2000 and . 6) Regulatory scaleup runs starting 2nd Qtr/2000.

Manufacturing cost for bulk drug is \$2,500/kg. Finished product will be determined by the site selection. The dosage strength is still to be determined but is estimated to be 100 ug or less. Cost estimates for ABT-594 have not been completed.

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

38

F. NON-CLINICAL

F.1 Toxicology

Relative to therapeutically efficacious doses in rats, ABT-594 has proven to be a relatively non-toxic product, aside from its emetic liability in monkeys. One-month toxicity studies in rat and monkey, three-month studies in rat, mouse and monkey, and six-month study in rat have been completed. A 12-month monkey study, and rat and mouse carcinogenicity studies are ongoing.

In rats, reduced body weights and food intake were observed at all dosages tested; these changes were judged likely to be due to a pharmacologic effect of the compound. Treatment-related findings in rat studies included increased bile acids, hematologic alterations, increased ALT and liver weights changes. In the six-month study, basophilic foci of cellular alteration were noted in livers of 1/20, 3/20 and 5/20 female animals from the 0.2, 0.5 and 2.0 mg base/kg/day dosage groups, respectively. The presence of foci of cellular alteration in rat livers is frequently related to the administration of carcinogenic compounds, but foci are by definition not neoplastic, and some types (e.g., the tigroid type seen in this study) are disputed as not truly representing preneoplastic lesions. They are regarded as proliferative, however, and a relationship to drug treatment suggests some sort of stimulus to cell replication. Any further works to investigate the mechanism of this liver finding will wait until the go/no go decision is made.

In monkeys, emesis and abnormal stool were seen; these were regarded as pharmacologic effects of this class of compound. Other drug-related effects included clinical signs and changes in hematology, serum chemistry, organ weights and histopathology. These findings were consistent with dehydration and exacerbation of a non-specific stress-related response.

A fertility and general reproduction study in rat, and teratogenicity studies in rat and rabbit have also been completed. There were no adverse effects on reproduction or embryo/fetal development. A peri- and postnatal study of ABT-594 in rat is currently ongoing. A juvenile rat study is schedule to start during the first quarter of 2001.

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Development Plan
ABT-594

39

Genetic toxicology studies conducted with ABT-594 included Ames assay, mouse lymphoma assay, *in vitro* cytogenetics assay and *in vivo* mouse micronucleus assay. ABT-594 was not found to be genotoxic in any of these assays. However, a mesylate impurity in the finished product was found to be weakly mutagenic in a single strain of bacteria (TA1535) in the Ames test. There are ongoing efforts in determining and setting safe limits of this impurity in future bulk drug lots.

All toxicology studies needed for the go/no go decision have been completed. As mentioned earlier, the only toxicology issue with ABT-594 at this time is the finding of basophilic foci in the rat liver. This finding should have no impact on labeling or milestone dates. The carcinogenicity studies are scheduled to be completed during the fourth quarter of 2001. If the findings in these studies are negative, no further toxicology work will be necessary and the milestone date of 12/01 for NDA filing should be met.

F.2 Metabolism

Animal ADME studies (mouse, rat and monkey) have shown that oral doses of tritiated ABT-594 drug are well absorbed, not extensively metabolized and excreted into the urine primarily as unchanged parent drug. The major biotransformation products have been identified and include oxidative and conjugated metabolites. *In vitro* studies with cDNA-expressed human cytochrome P450 (CYP) isoforms suggested that CYP2D6 could slowly catalyze the oxidative metabolism of ABT-594. However, the contribution of CYP2D6 to the total elimination of the drug is likely to be very small, suggesting that coadministered drugs which induce or inhibit CYP-dependent metabolism are not likely to alter the clearance of ABT-594 in humans. Other *in vitro* experiments showed that ABT-594 did not adversely inhibit the metabolism of a number of CYP selective substrates by human liver microsomes, suggesting little potential for clinically relevant drug/drug interactions. Studies in one or more species have shown that ABT-594 is not highly bound to plasma proteins and is uniformly distributed in human whole blood. Total radioactivity is widely distributed throughout rat tissues and demonstrated an affinity to bind to melanin containing tissues in pigmented rats.

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Development Plan
ABT-594

40

Placental and lacteal transfer studies of the radiolabeled drug in rats are scheduled to begin in the fourth quarter of 1999 or early in 2000. A limited tissue distribution study in pigmented rats is also planned to determine the half-life of total radioactivity in melanin-containing tissues. A radiolabeled study in normal human subjects is scheduled for 2000.

F3 Animal Pharmacology

The only animal pharmacology study ongoing that may be required later in the development of ABT-594 is a migraine study in Professor Peter Goadsby's Laboratory, Institute of Neurology, London. A report is anticipated in the 3rd quarter of 1999 on the effects of ABT-594 in a cat model of migraine.

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Development Plan
ABT-594

41

G. DEVELOPMENT COST AND SENSITIVITY ANALYSIS

The development milestones for ABT-594 are as follows:

Milestones	Date
PPCC Approval	12/96
Start Funding	1/97
Go/No Go Preclinical Safety	6/97
Start Phase I Europe	7/97
File IND (Liquid)	2/98
Start Phase II U.S.	7/98
Go/No Go Clinical Efficacy	9/99
File CTX/CTN	10/99
End of Phase II Mtg. w/FDA	11/99
Start Phase III U.S./Europe	12/99
Start Phase I Japan	2/00
Start Phase III Bridging Japan	1/01
File Europe - EMEA	12/01
File U.S. NDA - FDA	12/01
File Japan - Koseisho	6/02
Regulatory Approval U.S.	6/03

G.1 Base Case Scenario

The base case scenario consists of pursuing both the neuropathic pain and osteoarthritis indications. The Phase III program is aimed at obtaining indications for the treatment of pain associated with osteoarthritis and neuropathic pain. The Phase III program for osteoarthritis and neuropathic pain will each consist of three 600 patient Phase III pivotal studies to be conducted in the United States and one 600 Phase III study to be conducted in Europe to help facilitate regulatory approval and pricing in Europe. One 300 patient bridging study for each indication is also planned to be conducted in Japanese subjects.

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Analgesia Venture (6/23/99)
Development Plan
ABT-594

42

Planned Phase II and III Studies:

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	5	2700
Neuropathic Pain	1	150	5	2700
Cancer Pain	2	500	N/A	N/A
TOTAL	4	900	10	5400

* Does not include 2 long-term safety studies but does include Japan bridging studies.

Cost Through the NDA:

YEAR	COST
1999	29.9
2000	93.2
2001	50.5
TOTAL COST TO NDA	173.6

Breakdown by Year and Department:

	9/99 (to Go/NoGo)	1999	2000	2001 (to NDA)
PARD & CAPD	5.2	6.5	8.0	8.0
Drug Safety	3.8	4.7	5.0	2.5
Stats & DM	1.3	1.8	9.0	10.0
Venture Mgt	5.9	8.4	12.0	11.0
Grants	3.6	6.5	55.7	16.0
Other	1.8	2.0	3.5	3.0
TOTAL	21.6	29.9	93.2	50.5

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Development Plan
ABT-594

43

Breakdown by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEOARTHRITIS	TOTAL
1999	20.9	0	9.0	29.9
2000	36.9	29.2	27.1	93.2
2001	43.3	6.0	1.2	50.5
TOTAL	101.1	35.2	37.3	173.6

G.2 Downside Scenario (Funding Decrease)

Should funding need to be decreased, the strategy would be to eliminate one Phase III pivotal study from each indication. The negative aspect of this strategy adds more risk to the program, should one of the remaining two studies not statistically meet its efficacy outcome goal. The downside scenario is summarized in the following tables:

Downside Scenario Of Planned Phase II and III Studies

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	4	2100
Neuropathic Pain	1	150	4	2100
Cancer Pain	2	500	n/a	n/a
TOTAL	4	900	8	4200

Cost of Downside Scenario Through the NDA:

YEAR	COST
1999	27.7
2000	78.6
2001	54.4
TOTAL COST TO NDA	160.7

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Development Plan
ABT-594

44

Breakdown of Downside Scenario by Key Milestones and Department:

	9/99 (to Go/No Go)	1999	2000	2001 (to NDA)
PARD & CAPD	5.2	6.3	7.8	7.8
Drug Safety	3.8	4.7	5.0	2.5
Stats & DM	1.3	1.6	8.0	9.5
Venture Mgt	5.9	8.0	11.0	10.5
Grants	3.6	7.5	49.0	15.2
Other	1.8	1.8	3.5	3.0
TOTAL	21.6	27.9	84.3	48.5

Breakdown of Downside Scenario by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEOARTHRITIS	TOTAL
1999	20.9	0	7.0	27.9
2000	36.9	25.2	22.2	84.3
2001	43.3	4.0	1.2	48.5
TOTAL	101.1	29.2	30.4	160.7

G.3 Upside Scenario (Funding Increase)

The development strategy should additional funding become available would be to pursue an indication for the treatment of cancer pain. Three 600 patient Phase III pivotal studies would be planned for the U.S. and one would be planned for Europe.

A summary of the upside scenario is presented in the following tables:

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Development Plan
ABT-594

45

Upside Scenario of Planned Phase II and III Studies:

INDICATION	PHASE II	PHASE II	PHASE III	PHASE III
	# Studies	# Patients	# Studies	# Patients
Osteoarthritis	1	250	5	2700
Neuropathic Pain	1	150	5	2700
Cancer Pain	2	500	5	2700

Cost of Upside Scenario Through the NDA:

YEAR	COST
1999	29.9
2000	93.2
2001	69.0
2002	16.8
TOTAL COST TO NDA	208.9

Breakdown of Upside Scenario by Key Milestones and Department:

	9/99 (to Go/NoGo)	1999	2000	2001 (to NDA)	2002 (to SNDA)
PARD & CAPD	5.2	6.5	8.0	8.0	0.5
Drug Safety	3.8	4.7	5.0	2.5	0
Stats & DM	1.3	1.8	9.0	10.0	2.0
Venture Mgt	5.9	8.4	12.0	11.0	2.0
Grants	3.6	6.5	55.7	34.5	11.3
Other	1.8	2.0	3.5	3.0	1.0
TOTAL	21.6	29.9	93.2	69.0	16.8

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Development Plan
ABT-594

46

Breakdown of Upside Scenario by Indication:

YEAR	BASE PROGRAM	NEUROPATHIC PAIN	OSTEO-ARTHRITIS	CANCER PAIN	TOTAL
1999	20.9	0	9.0	0	29.9
2000	36.9	29.2	27.1	0	93.2
2001	43.0	6.0	1.2	18.5	69.0
2002	0	0	0	16.8	16.8
TOTAL	101.1	35.2	37.3	35.3	208.9

IN/R-S/1/ABT594/DEVPLANS/699/DEVPLAN

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Project Summary by Dept.

06/17/99

Analgesia

Project ABT-594

Version Plan

Sponsor All

Indication Pain (General)

Formulation Oral Solid

Dept. Advanced Technology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 10,657	\$ 42,912	\$ 53,569
1997	\$ 235,263	\$ 250,205	\$ 491,455	\$ 598,745	\$ 1,575,670
1998	\$ 168,935	\$ 167,725	\$ 175,046	\$ 165,493	\$ 677,200
1999	\$ 166,156	\$ 162,461	\$ 161,738	\$ 159,917	\$ 650,273
2000	\$ 146,079	\$ 146,079	\$ 111,761	\$ 99,792	\$ 503,714
2001	\$ 493,585	\$ 223,384	\$ 43,140	\$ 15,976	\$ 776,087
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Analytical Departments

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 483,095	\$ 232,800	\$ 273,694	\$ 870,408	\$ 1,859,998
1998	\$ 439,774	\$ 1,052,472	\$ 609,632	\$ 341,846	\$ 2,443,725
1999	\$ 378,395	\$ 171,735	\$ 561,971	\$ 238,276	\$ 1,350,379
2000	\$ 304,339	\$ 159,215	\$ 73,450	\$ 65,257	\$ 602,262
2001	\$ 718,730	\$ 354,731	\$ 176,462	\$ 63,471	\$ 1,313,395
2002	\$ 120,694	\$ 122,035	\$ 123,376	\$ 123,376	\$ 489,484
2003	\$ 120,694	\$ 116,588	\$ 23,152	\$ 23,152	\$ 283,588
2004	\$ 22,900	\$ 21,294	\$ 10,215	\$	\$ 54,410

Dept. Analytical Development

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 407,076	\$ 80,086	\$ 169,094	\$ 544,254	\$ 1,200,512
1998	\$ 323,136	\$ 526,208	\$ 269,145	\$ 282,787	\$ 1,401,279
1999	\$ 501,870	\$ 513,551	\$ 609,296	\$ 125,345	\$ 1,750,064
2000	\$	\$	\$	\$	\$
2001	\$	\$	\$	\$ 1,048,834	\$ 1,048,834
2002	\$ 95,403	\$	\$	\$	\$ 95,403
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Page: 1

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ABBT 0019051

Project summary continues ...

Dept. Animal Services

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 4,750	\$ 8,727	\$ 13,477
1997	\$ 22,815	\$ 97,671	\$ 164,209	\$ 106,901	\$ 391,599
1998	\$ 34,635	\$ 160,359	\$ 217,042	\$ 251,239	\$ 663,275
1999	\$ 130,181	\$ 121,848	\$ 98,343	\$ 89,769	\$ 440,143
2000	\$ 88,793	\$ 88,793	\$ 82,362	\$ 29,879	\$ 289,828
2001	\$	\$	\$	\$	\$
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. CAPD

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 752,697	\$ 94,691	\$ 270,305	\$ 1,154,305	\$ 2,272,000
1998	\$ 1,024,705	\$ 1,189,996	\$ 582,495	\$ 582,495	\$ 3,379,692
1999	\$ 1,751,028	\$ 627,279	\$ 714,672	\$ 221,327	\$ 3,314,307
2000	\$	\$	\$	\$	\$
2001	\$	\$	\$	\$ 6,520,989	\$ 6,520,989
2002	\$ 593,010	\$	\$	\$	\$ 593,010
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. CCM - Pain Management

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ -	\$ 22,874	\$ 1,428,470	\$ 1,011,771	\$ 2,463,116
1998	\$ 134,510	\$ 671,568	\$ 2,437,072	\$ 1,811,126	\$ 5,054,278
1999	\$ 1,930,518	\$ 2,079,560	\$ 1,955,284	\$ 9,995,221	\$ 15,960,585
2000	\$ 14,055,072	\$ 20,758,630	\$ 20,770,536	\$ 20,181,969	\$ 75,766,207
2001	\$ 11,133,093	\$ 6,873,167	\$ 7,064,646	\$ 3,255,536	\$ 28,326,443
2002	\$ 559,905	\$ 402,769	\$ 382,479	\$ 382,479	\$ 1,727,633
2003	\$ 374,164	\$ 378,321	\$ 18,687	\$ 41,284	\$ 812,458
2004	\$	\$	\$	\$	\$

Dept. Clinical Packaging

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$	\$ 42,205	\$ 51,786	\$ 7,984	\$ 101,976
1998	\$ 1,041	\$ 148,437	\$ 213,028	\$ 76,259	\$ 438,766
1999	\$ 59,747	\$ 96,049	\$ 25,686	\$ 570,825	\$ 752,309
2000	\$ 702,160	\$ 436,549	\$ 381,020	\$ 269,264	\$ 1,788,994
2001	\$ 238,371	\$ 90,440	\$ 88,339	\$ 49,013	\$ 466,165
2002	\$ 6,254	\$ 6,324	\$ 6,393	\$ 6,393	\$ 25,366
2003	\$ 6,254	\$ 6,324	\$ 69	\$	\$ 12,648
2004	\$	\$	\$	\$	\$

Page : 2

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ABBT 0019052

Project summary continues ...

Dept. Data Mgmt

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 10,482	\$ 10,482
1997	\$ 11,122	\$ 49,418	\$ 118,915	\$ 118,489	\$ 297,946
1998	\$ 92,007	\$ 129,467	\$ 490,658	\$ 431,918	\$ 1,144,052
1999	\$ 154,737	\$ 179,015	\$ 387,325	\$ 512,108	\$ 1,233,185
2000	\$ 1,393,065	\$ 1,949,078	\$ 1,820,484	\$ 2,246,111	\$ 7,408,740
2001	\$ 2,877,738	\$ 1,303,668	\$ 945,111	\$ 1,568,880	\$ 6,695,399
2002	\$ 323,891	\$ 63,448	\$ 56,784	\$ 56,784	\$ 500,910
2003	\$ 55,550	\$ 56,167	\$ 491,653	\$ 12,295	\$ 615,667
2004	\$	\$	\$	\$	\$

Dept. Drug Analysis

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 96,583	\$ 58,121	\$ 102,414	\$ 176,405	\$ 433,525
1998	\$ 115,928	\$ 110,053	\$ 182,340	\$ 133,862	\$ 542,185
1999	\$ 93,699	\$ 126,122	\$ 138,102	\$ 100,533	\$ 458,457
2000	\$ 130,094	\$ 547,815	\$ 577,273	\$ 370,042	\$ 1,625,226
2001	\$ 205,567	\$ 75,677	\$ 10,085	\$ 4,805	\$ 296,136
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Formulation Departments

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 117,100	\$ 149,552	\$ 78,811	\$ 218,372	\$ 563,836
1998	\$ 161,127	\$ 280,924	\$ 269,205	\$ 167,706	\$ 878,963
1999	\$ 158,945	\$ 160,711	\$ 131,809	\$ 238,162	\$ 689,628
2000	\$ 408,672	\$ 157,660	\$ 33,808	\$ 33,808	\$ 633,949
2001	\$ 28,288	\$ 90,896	\$ 103,518	\$ 71,467	\$ 294,171
2002	\$ 26,962	\$ 27,262	\$ 27,561	\$ 27,561	\$ 109,347
2003	\$ 26,962	\$ 25,764	\$	\$	\$ 52,726
2004	\$	\$	\$	\$	\$

Dept. Formulation Development

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 117,100	\$ 149,552	\$ 78,811	\$ 218,372	\$ 563,836
1998	\$ 161,127	\$ 280,924	\$ 269,205	\$ 167,706	\$ 878,963
1999	\$ 158,945	\$ 160,711	\$ 131,809	\$ 238,162	\$ 689,628
2000	\$ 408,672	\$ 605,963	\$ 289,626	\$ 44,067	\$ 1,348,330
2001	\$ 38,324	\$ 90,034	\$ 89,016	\$ 71,467	\$ 288,842
2002	\$ 420,572	\$ 577,286	\$ 37,463	\$ 37,463	\$ 1,072,786
2003	\$ 36,648	\$ 35,558	\$	\$	\$ 72,207
2004	\$	\$	\$	\$	\$

Page : 3

CONFIDENTIAL

ABBT 0019053

Project summary continues ...

Dept. Integrative Pharmacology*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 96,288	\$ 95,954	\$ 95,604	\$ 56,721	\$ 344,569
1998	\$ 11,369	\$ 11,495	\$ 11,622	\$ 11,116	\$ 45,604
1999	\$ 11,369	\$ 11,495	\$ 11,622	\$ 11,116	\$ 45,604
2000	\$ 11,338	\$ 11,338	\$ 11,463	\$ 11,463	\$ 45,604
2001	\$	\$	\$	\$	\$
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Metabolism*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 59,225	\$ 59,225
1997	\$ 201,936	\$ 152,297	\$ 100,463	\$ 178,873	\$ 633,571
1998	\$ 234,032	\$ 152,999	\$ 139,676	\$ 80,553	\$ 607,262
1999	\$ 59,016	\$ 36,075	\$ 133,191	\$ 90,445	\$ 318,729
2000	\$ 87,821	\$ 72,865	\$ 39,932	\$ 13,147	\$ 213,767
2001	\$ 48,662	\$ 21,340	\$ 3,361	\$ 1,601	\$ 74,966
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. PARD Management*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
------	-------------	-------------	-------------	-------------	--------

..... No Data for This Combination

Dept. Pathology*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 9,228	\$ 75,235	\$ 84,463
1997	\$ 135,807	\$ 182,025	\$ 166,772	\$ 94,872	\$ 579,478
1998	\$ 129,052	\$ 77,012	\$ 64,790	\$ 68,506	\$ 339,361
1999	\$ 120,131	\$ 52,991	\$ 70,993	\$ 74,932	\$ 319,048
2000	\$ 22,538	\$ 21,648	\$ 20,080	\$ 104,938	\$ 169,205
2001	\$ 226,892	\$ 290,092	\$ 264,241	\$	\$ 781,226
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Page : 4

CONFIDENTIAL

ABBT 0019054

Project summary continues ...

Dept. Pharm Analysis & Stability*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 67,284	\$ 111,476	\$ 65,784	\$ 113,926	\$ 358,472
1998	\$ 73,488	\$ 506,763	\$ 352,189	\$ 95,480	\$ 1,027,922
1999	\$ 91,079	\$ 92,091	\$ 98,748	\$ 162,134	\$ 444,054
2000	\$ 260,237	\$ 375,294	\$ 181,892	\$ 57,453	\$ 874,878
2001	\$ 602,346	\$ 262,531	\$ 63,422	\$ 44,310	\$ 972,611
2002	\$ 334,426	\$ 274,134	\$ 125,434	\$ 125,434	\$ 859,429
2003	\$ 122,707	\$ 118,623	\$ 3,991	\$ 3,991	\$ 249,314
2004	\$ 3,948	\$ 3,145	\$ 768	\$	\$ 7,862

Dept. PK/Biopharmaceutics*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1998	\$ 3,502	\$ 6,128	\$ 12,947	\$ 37,924	\$ 60,503
1999	\$ 49,153	\$ 49,487	\$ 44,945	\$ 37,292	\$ 180,879
2000	\$ 15,091	\$ 110,013	\$ 204,028	\$ 148,536	\$ 477,669
2001	\$ 31,910	\$ 7,771	\$	\$	\$ 39,682
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Process Development*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
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..... No Data for This Combination

Dept. R&D Records Center*View* **Total Cost**

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 370	\$ 370
1997	\$ 7,090	\$ 7,618	\$ 9,609	\$ 9,541	\$ 33,860
1998	\$ 9,473	\$ 22,765	\$ 54,322	\$ 51,595	\$ 138,156
1999	\$ 50,081	\$ 51,206	\$ 52,949	\$ 39,970	\$ 194,207
2000	\$ 46,494	\$ 49,209	\$ 49,231	\$ 44,177	\$ 189,112
2001	\$ 35,891	\$ 38,918	\$ 17,601	\$ 4,696	\$ 97,108
2002	\$ 17,325	\$ 15,951	\$ 15,646	\$ 15,646	\$ 64,569
2003	\$ 15,306	\$ 15,476	\$ 283	\$ 801	\$ 31,868
2004	\$	\$	\$	\$	\$

Page : 5

CONFIDENTIAL

ABBT 0019055

Project summary continues ...

Dept. Regulatory Affairs

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 8,539	\$ 8,634	\$ 603	\$ 508	\$ 18,285
1998	\$ 497	\$ 5,821	\$ 16,819	\$ 16,819	\$ 39,958
1999	\$ 16,454	\$ 16,636	\$ 16,819	\$ 24,010	\$ 73,921
2000	\$ 23,749	\$ 23,749	\$ 24,010	\$ 23,844	\$ 95,353
2001	\$ 22,991	\$ 28,877	\$ 352,029	\$ 352,883	\$ 756,782
2002	\$ 20,704	\$ 366,310	\$ 21,164	\$ 21,164	\$ 429,342
2003	\$ 20,704	\$ 20,934	\$	\$	\$ 41,638
2004	\$	\$	\$	\$	\$

Dept. Res Services/Planning

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$ 34,031	\$ 34,410	\$ 1,958	\$ 1,580	\$ 71,980
1998	\$ 1,545	\$ 3,187	\$ 6,561	\$ 6,561	\$ 17,857
1999	\$ 6,419	\$ 6,490	\$ 6,561	\$ 5,169	\$ 24,640
2000	\$ 5,112	\$ 5,112	\$ 5,169	\$ 4,653	\$ 20,048
2001	\$ 3,510	\$ 3,549	\$ 1,443	\$ 796	\$ 9,300
2002	\$ 4,215	\$ 4,262	\$ 4,309	\$ 4,309	\$ 17,096
2003	\$ 4,215	\$ 4,262	\$	\$	\$ 8,478
2004	\$	\$	\$	\$	\$

Dept. Research QA

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$	\$ 4,135	\$ 4,135
1997	\$ 12,927	\$ 32,632	\$ 21,416	\$ 20,834	\$ 87,811
1998	\$ 33,356	\$ 26,304	\$ 14,844	\$ 32,379	\$ 106,885
1999	\$ 59,688	\$ 38,634	\$ 39,224	\$ 58,548	\$ 196,096
2000	\$ 81,622	\$ 144,534	\$ 170,128	\$ 176,115	\$ 572,399
2001	\$ 117,854	\$ 119,325	\$ 117,045	\$ 361,617	\$ 715,842
2002	\$ 27,202	\$ 178,063	\$ 846	\$ 846	\$ 206,959
2003	\$ 828	\$ 837	\$	\$	\$ 1,665
2004	\$	\$	\$	\$	\$

Dept. Statistics

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1997	\$	\$ 2,084	\$ 5,272	\$ 6,647	\$ 14,004
1998	\$ 7,491	\$ 19,765	\$ 51,998	\$ 71,949	\$ 151,204
1999	\$ 60,239	\$ 72,090	\$ 89,504	\$ 137,008	\$ 358,843
2000	\$ 151,519	\$ 252,420	\$ 315,189	\$ 206,279	\$ 925,408
2001	\$ 227,941	\$ 330,952	\$ 43,362	\$ 187,602	\$ 789,859
2002	\$ 228,378	\$ 42,221	\$ 4,792	\$ 4,792	\$ 280,185
2003	\$ 4,688	\$ 4,740	\$ 29,062	\$ 41,966	\$ 80,458
2004	\$	\$	\$	\$	\$

Page : 6

CONFIDENTIAL .

ABBT 0019056

Project summary continues ...

Dept. Statistics - Pre-Clinical

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 5,297	\$ 23,624	\$ 28,921
1997	\$ 71,773	\$ 17,663	\$ 9,517	\$ 35,345	\$ 134,300
1998	\$ 64,175	\$ 36,290	\$ 14,459	\$ 13,835	\$ 128,762
1999	\$ 16,651	\$ 8,757	\$ 10,622	\$ 10,311	\$ 46,342
2000	\$	\$	\$	\$ 6,592	\$ 6,592
2001	\$ 15,316	\$ 19,583	\$ 17,838	\$	\$ 52,738
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

Dept. Toxicology

View Total Cost

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Totals
1996	\$	\$	\$ 30,760	\$ 64,068	\$ 94,828
1997	\$ 235,198	\$ 190,468	\$ 327,670	\$ 309,600	\$ 1,062,937
1998	\$ 194,431	\$ 230,326	\$ 414,177	\$ 379,115	\$ 1,218,050
1999	\$ 329,377	\$ 214,823	\$ 183,067	\$ 173,756	\$ 901,024
2000	\$ 137,780	\$ 134,218	\$ 124,496	\$ 64,696	\$ 461,192
2001	\$ 45,378	\$ 58,018	\$ 52,848	\$	\$ 156,245
2002	\$	\$	\$	\$	\$
2003	\$	\$	\$	\$	\$
2004	\$	\$	\$	\$	\$

by Department Project Totals

View Total Cost

Sponsor All

Year	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter	Grand Totals
1996	\$	\$	\$ 60,694	\$ 288,781	\$ 349,475
1997	\$ 3,113,735	\$ 2,062,447	\$ 4,032,642	\$ 5,854,464	\$ 15,063,290
1998	\$ 3,419,347	\$ 5,817,001	\$ 6,869,283	\$ 5,278,281	\$ 21,383,914
1999	\$ 6,353,889	\$ 5,049,829	\$ 5,674,293	\$ 13,314,345	\$ 30,392,357
2000	\$ 18,480,257	\$ 26,050,190	\$ 25,285,946	\$ 24,202,091	\$ 94,018,486
2001	\$ 17,112,397	\$ 10,282,961	\$ 9,453,516	\$ 13,623,953	\$ 50,472,828
2002	\$ 2,778,949	\$ 2,080,071	\$ 806,253	\$ 806,253	\$ 6,471,526
2003	\$ 788,725	\$ 783,599	\$ 566,901	\$ 123,492	\$ 2,262,719
2004	\$ 26,849	\$ 24,439	\$ 10,984	\$	\$ 62,272

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Page : 7

CONFIDENTIAL

ABBT 0019057

Project Assumption Report

Project Name

Project Number

Report As Of: Jun 17, 199

ABT-594

G0 143010

Active

Phase : 0

Activity

Protocol

Activity Start

Activity End

No. Patients

No. Sites

Manpower PMP

Direct Dollars

Grant Dollars

Comments

Prepare ISS/ISE

Apr 1, 2001

Sep 15, 2001

0

0

NDA Preparation

Jul 1, 2001

Nov 29, 2001

0

0

NDA Filing

Dec 1, 2001

Dec 1, 2001

0

0

Active

Phase : 1

Activity

Protocol

Activity Start

Activity End

No. Patients

No. Sites

Manpower PMP

Direct Dollars

Grant Dollars

Comments

Ph I Single Dose (M97-676)

M97676

Jul 1, 1997

Sep 15, 1997

80

1

England

Ph I Multiple Dose (M97-743)

M97743

Sep 29, 1997

Jan 12, 1998

92

1

Netherlands

Ph I Effect of Food (M97-787)

M97787

Jun 22, 1998

Jul 23, 1998

12

1

U.S.

Ph I Bio (P/B vs. SEC) (M97-706)

Jun 22, 1998

Aug 22, 1998

24

1

Scotland

Ph I 14 Day 75mcg BID (M98-907)

M98907

Aug 25, 1998

Sep 24, 1998

12

1

Ph I Pain Model (M98-899)

M98899

Sep 22, 1998

Nov 21, 1998

12

1

Scotland

Ph I Bio M98-984 (HGC vs SEC)

Mar 22, 1999

May 21, 1999

24

1

U.S.

Ph I Bio M99-043 (75ug HGC)

M99043

Jun 30, 1999

Aug 31, 1999

24

1

Ph I Rising Multi HCG BID Doses

Jul 12, 1999

Sep 10, 1999

50

1

USA

Human Metabolism (M98-986)

M98971

Jan 1, 2000

Apr 30, 2000

6

1

U.S.

Ph I Pilot Bio Study (Ph III vs Comm

Jan 10, 2000

Mar 10, 2000

24

0

U.S.

Ph I Interaction # 1

Jan 10, 2000

Mar 10, 2000

32

1

U.S.

Ph I Cardiovascular Safety

Feb 1, 2000

May 1, 2000

32

1

Ph I Single Dose PK in Japanese

Feb 1, 2000

Apr 1, 2000

60

3

Japan

Ph I PK in Elderly Subjects

M98986

Feb 15, 2000

Apr 29, 2000

48

1

U.S.

Ph I PK Renal Impaired

Feb 15, 2000

May 15, 2000

32

1

U.S.

Ph I PK in Smokers

Apr 1, 2000

Jun 30, 2000

48

1

U.S.

Ph I PK Hepatic Impaired

Apr 1, 2000

Jun 30, 2000

32

1

U.S.

Ph I Interaction # 2

Apr 1, 2000

May 31, 2000

32

1

U.S.

Page: 1

CONFIDENTIAL

ABBT 0019058

Project Assumption Report

Project Name	Project Number	Report As Of: Jun 17, 199			
ABT-594	G0 143010				
Ph I Interaction # 3	May 1, 2000	Jun 30, 2000	32	1 U.S.	
Ph I Multi Dose PK in Japanese	Jun 1, 2000	Aug 30, 2000	60	2	
Ph I Interaction # 4	Jun 1, 2000	Jul 31, 2000	32	1 U.S.	
Ph I Interaction # 5	Jul 1, 2000	Aug 30, 2000	32	1	
Ph I Effect of Food in Japanese	Aug 1, 2000	Sep 15, 2000	24	1 U.S.	
Ph I Interaction # 6	Aug 1, 2000	Sep 30, 2000	32	1	
Ph I Bio (Ph III Form vs Commercial)	Oct 1, 2000	Nov 29, 2000	32	1 U.S.	
Active					
Phase : 2					
Activity	Protocol	Activity Start	Activity End	No. Patents	No. Sites
Ph II Molar Extraction (M97-772)	M97772	Jun 25, 1998	Oct 23, 1998	290	1 U.S.
Ph II Molar Extraction (M98-897)	M98897	Aug 10, 1998	Sep 24, 1998	45	1
Ph II Osteoarthritis (M98-826)	M98826	Oct 26, 1998	Aug 22, 1999	250	20 U.S.
Ph II Neuropathic Pain (M98-833)	M98833	Oct 28, 1998	Aug 24, 1999	150	10 U.S.
Ph II Cancer Pain		May 1, 2000	Feb 1, 2001	250	20 U.S.
Ph II Cancer Pain		May 7, 2000	Feb 7, 2001	250	20 U.S.
Active					
Phase : 3					
Activity	Protocol	Activity Start	Activity End	No. Patents	No. Sites
Ph III Osteoarthritis (Pivotal I)		Dec 1, 1999	Nov 30, 2000	600	30 U.S.
Ph III Osteoarthritis (Pivotal II)		Dec 2, 1999	Dec 1, 2000	600	30 U.S.
Ph III Osteoarthritis (Pivotal III)		Dec 3, 1999	Nov 27, 2000	600	30 U.S.
Ph III Osteoarthritis Europe		Dec 5, 1999	Jan 8, 2001	600	40 Europe
Ph III Long Term Safety Europe		Dec 15, 1999	Jul 1, 2003	300	60 Europe
Ph III Long Term Safety		Dec 15, 1999	Jul 1, 2003	600	150 U.S.
Ph III Neuropathic Pain (Pivotal I)		Mar 1, 2000	Mar 29, 2001	600	30 U.S.
Ph III Neuropathic Pain (Pivotal II)		Mar 8, 2000	Feb 9, 2001	600	30 U.S.
Ph III Neuropathic Pain (Pivotal III)		Mar 15, 2000	Feb 15, 2001	600	30 U.S.

Page : 2

CONFIDENTIAL

ABBT 0019059

Project Assumption Report

Project Name	Project Number	Report As Of: Jun 17, 199				
ABT-594	G0 143010					
Ph III Neuropathic Pain Europe	Mar 21, 2000	Jan 26, 2001	600	40 Europe		
Ph III Osteoarthritis (Bridging) Japan	Oct 1, 2000	Sep 6, 2001	300	15 Japan		
Ph III Neuropathic (Bridging) Japan	Nov 1, 2000	Sep 27, 2001	300	15 Japan		
Ph IIIB Pricing Study U.S.	Feb 1, 2001	Oct 29, 2001	500	25 U.S.		
Ph IIIB Pricing Study Australia	Mar 1, 2001	Nov 26, 2001	500	25 Australia		
Ph IIIB Pricing Study Canada	Mar 1, 2001	Nov 26, 2001	500	25 Canada		
Ph IIIB Pricing Study Europe	Apr 1, 2001	Dec 27, 2001	500	25 Europe		

Page : 3

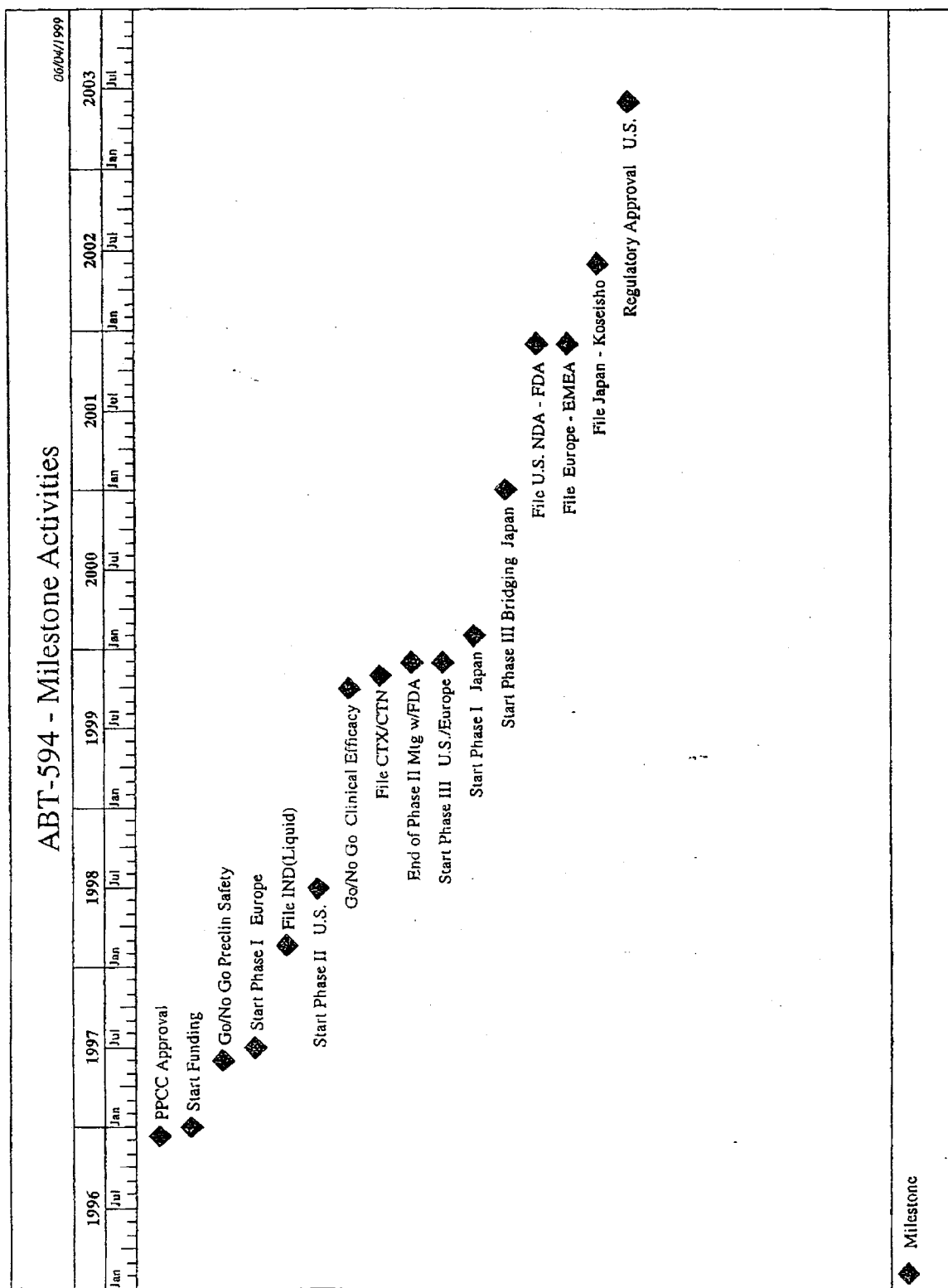
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ABBT 0019060



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ABBT 0019061



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ABT 0019062

Activity Listing

06/17/99

Sponsor Milestone		Project ABT-594		Indication Pain (General)			
Version Plan		Project N G0 143010		Formulation Oral Solid			
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code	
PPCC Approval	NKMSA101	12/10/1996	12/10/1996	12/10/1996	12/10/1996	C	
Start Funding	NKMSB102	01/01/1997	01/01/1997	01/01/1997	01/01/1997	C	
Go/No Go Preclin Safety	NKMSC103	06/01/1997	06/01/1997	06/01/1997	06/01/1997	C	
Start Phase I. Europe	NKMSP301	07/01/1997	07/01/1997	07/01/1997	07/01/1997	C	
File IND(Liquid)	NKMSD104	02/19/1998	02/19/1998	02/19/1998	02/19/1998	C	
Start Phase II U.S.	NKMSD001	07/01/1998	07/01/1998	07/01/1998	07/01/1998	C	
Go/No Go Clinical Efficacy	NKMSD002	09/30/1999	09/30/1999	09/30/1999	09/30/1999	A	
File CTX/CTN	NKMSD021	10/31/1999	10/31/1999	10/31/1999	10/31/1999	A	
End of Phase II Mtg w/FDA	NKMSD020	11/30/1999	11/30/1999	11/30/1999	11/30/1999	A	
Start Phase III U.S./Europe	NKMSD004	12/01/1999	02/28/2000	02/28/2000	02/28/2000	A	
Start Phase I Japan	NKMSD016	02/01/2000	02/01/2000	02/01/2000	02/01/2000	A	
Start Phase III Bridging Japan	NKMSD017	01/01/2001	01/01/2001	01/01/2001	01/01/2001	A	
File Europe - EMEA	NKMSD006	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A	
File U.S. NDA - FDA	NKMSL112	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A	
File Japan - Koscisho	NKMSD019	06/01/2002	06/01/2002	06/01/2002	06/01/2002	A	
Regulatory Approval U.S.	NKMSD007	06/01/2003	06/01/2003	06/01/2003	06/01/2003	A	

Page : 1

CONFIDENTIAL

ABBT 0019063

McCarthy Deposition Exhibit 6

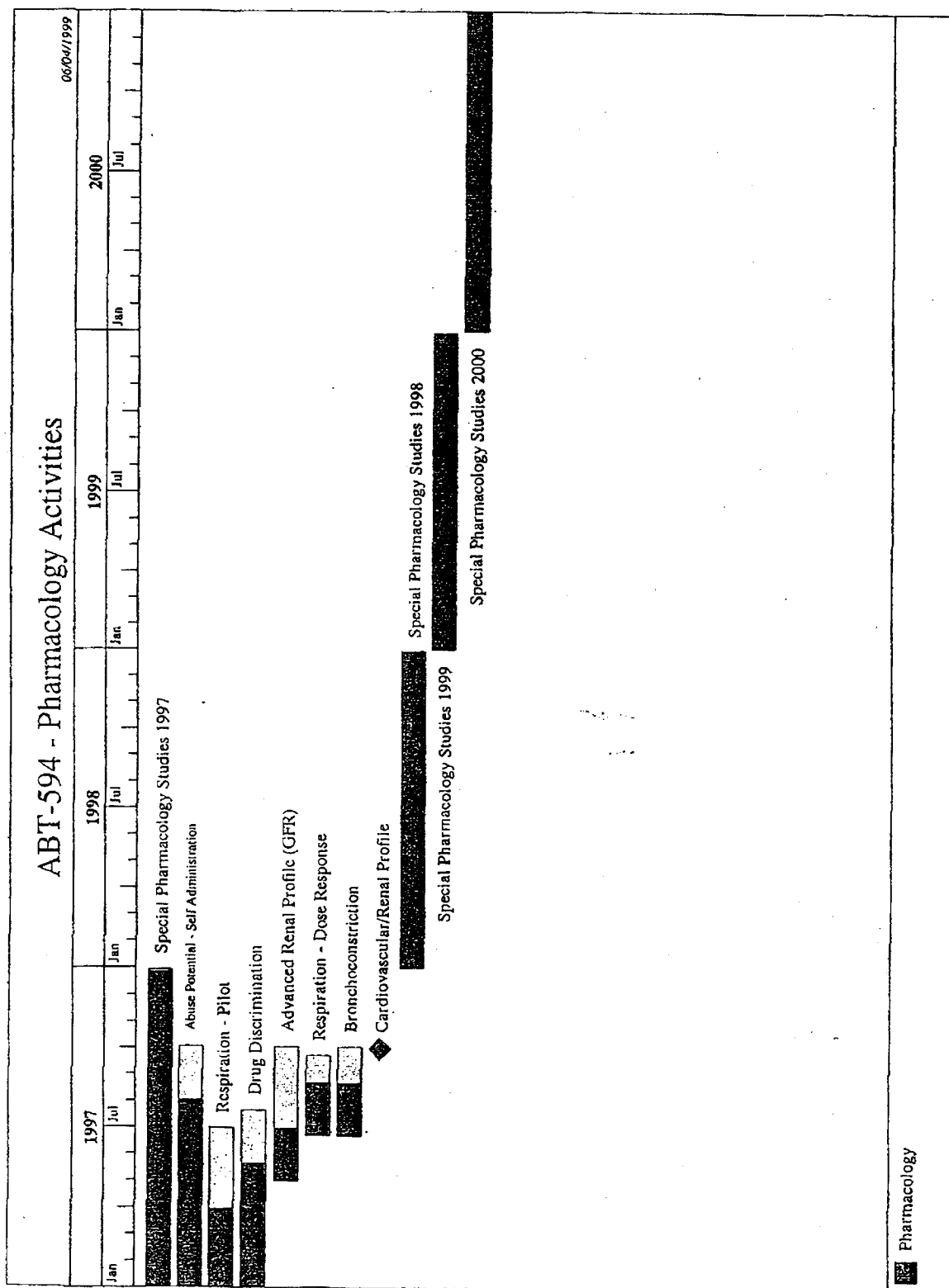
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Part 3



CONFIDENTIAL

ABBT 0019064



CONFIDENTIAL

ABBT 0019065

Activity Listing

06/17/99

Sponsor Pharmacology		Project ABT-594		Indication Pain (General)			
Version	Plan	Project N	G0 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Respiration - Pilot		NKALD001	01/01/1997	04/01/1997	05/01/1997	07/01/1997	C
Drug Discrimination		NKALLB01	01/01/1997	05/21/1997	06/21/1997	07/21/1997	C
Abuse Potential - Self Administration		NKALLB02	01/01/1997	08/01/1997	09/01/1997	10/01/1997	C
Special Pharmacology Studies 1997		NKALLB03	01/01/1997	12/27/1997	12/27/1997	12/27/1997	C
Advanced Renal Profile (GFR)		NKALD004	05/01/1997	07/01/1997	08/01/1997	10/01/1997	C
Respiration - Dose Response		NKALD005	06/23/1997	08/23/1997	08/23/1997	09/22/1997	C
Bronchoconstriction		NKALD006	06/23/1997	08/23/1997	09/01/1997	10/01/1997	C
Cardiovascular/Renal Profile		NKALD002	10/01/1997	10/01/1997	10/01/1997	10/01/1997	C
Special Pharmacology Studies 1998		NKALD008	01/01/1998	12/27/1998	12/27/1998	12/27/1998	C
Special Pharmacology Studies 1999		NKALD007	01/01/1999	12/27/1999	12/27/1999	12/27/1999	A
Special Pharmacology Studies 2000		NKALD010	01/01/2000	12/31/2000	12/31/2000	12/31/2000	A

Page : 1

CONFIDENTIAL

ABBT 0019066



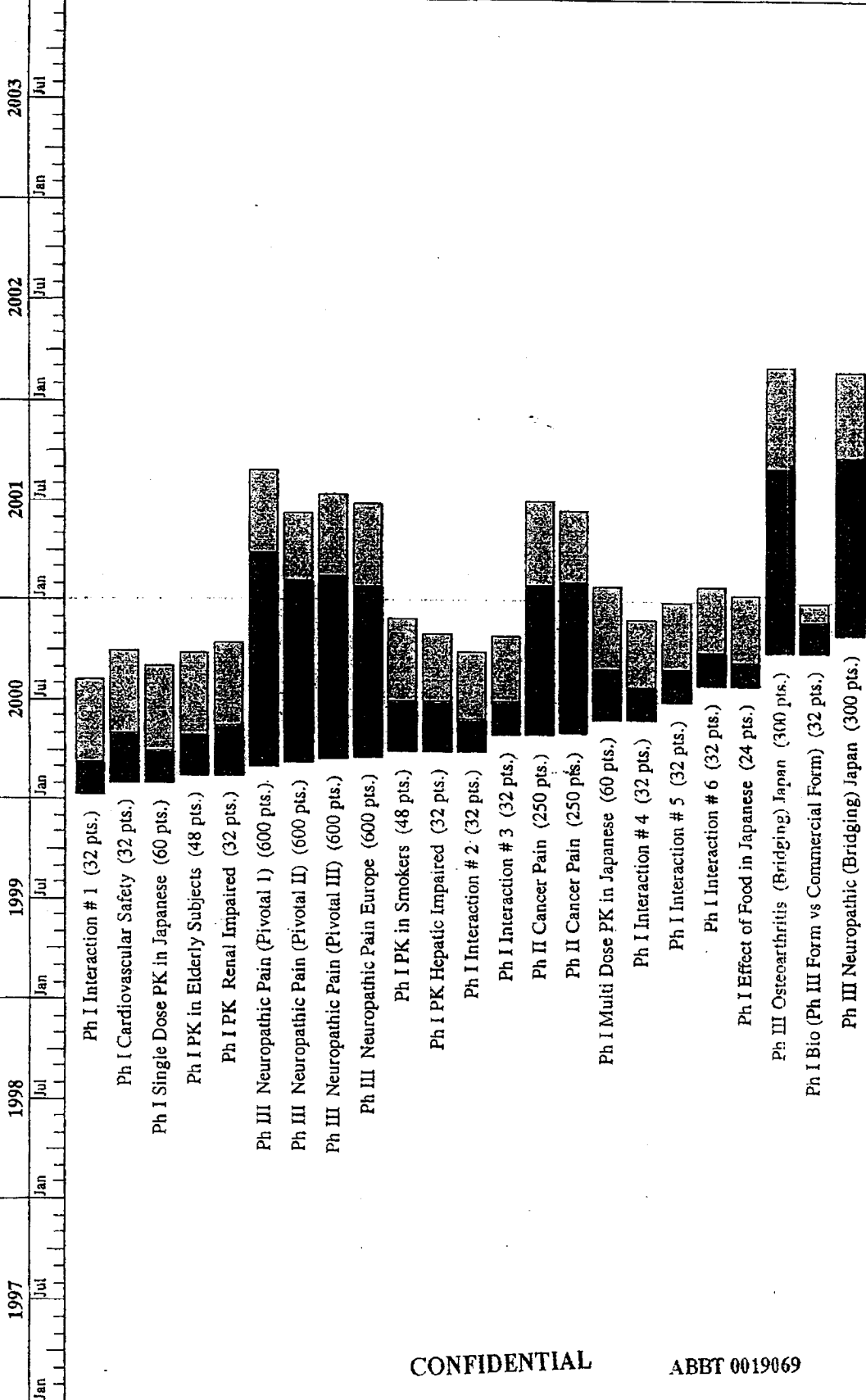
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ABBT 0019067



ABT-594 - Clinical Activities

06/17/1999



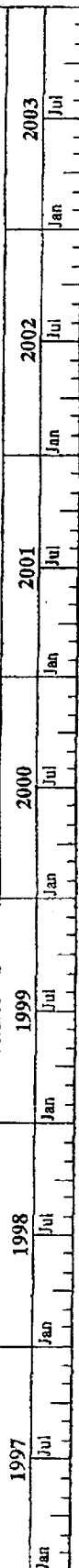
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ABBT 0019069

Clinical

ABT-594 - Clinical Activities

06/18/1999



Ph IIIB Pricing Study U.S. (500 pts.)

Ph IIIB Pricing Study Canada (500 pts.)

Ph IIIB Pricing Study Australia (500 pts.)

Prepare ISS/ISE

Ph IIIB Pricing Study Europe (500 pts.)

NDA / EMEA Preparation

NDA / EMEA Filing

File Koseicho - Japan

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ABBT 0019070

Clinical

Page 3 of 3

Activity Listing

06/17/99

Sponsor Clinical	Project	ABT-594	Indication	Pair: (General)		
Version Plan	Project N	G0 143010	Formulation	Oral Solid		
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Ph I Single Dose (M97-676)	NKACP103	07/01/1997	09/15/1997	02/08/1998	05/29/1999	A
Ph I Multiple Dose (M97-743)	NKACP129	09/29/1997	01/12/1998	08/07/1998	07/03/1999	A
IND Filing (Liquid)	NKACPY09	02/09/1998	02/09/1998	02/09/1998	02/09/1998	C
Ph I Effect of Food (M97-787)	NKACP104	06/22/1998	07/23/1998	08/22/1998	07/23/1999	A
Ph I Bio (PIB vs. SEC) (M97-706)	NKACP105	06/22/1998	08/22/1998	09/21/1998	08/12/1999	A
Ph II Molar Extraction (M97-772)	NKACP216	06/25/1998	10/23/1998	11/22/1998	09/01/1999	A
Ph II Molar Extraction (M98-897)	NKACD076	08/10/1998	09/24/1998	10/24/1998	10/01/1999	A
Ph I 14 Day 75mcg BID (M98-907)	NKACD077	08/25/1998	09/24/1998	10/24/1998	11/01/1999	A
IND Filing (Solid)	NKACD068	09/10/1998	09/10/1998	09/10/1998	09/10/1998	C
Ph I Pain Model (M98-899)	NKACD074	09/22/1998	11/21/1998	12/21/1998	12/01/1999	A
Ph II Osteoarthritis (M98-826)	NKACP202	10/26/1998	08/22/1999	09/21/1999	02/18/2000	A
Ph II Neuropathic Pain (M98-833)	NKACP204	10/28/1998	08/24/1999	09/23/1999	03/22/2000	A
Ph I Bio M98-984 (HGC vs SEC)	NKACD062	03/22/1999	05/21/1999	06/20/1999	10/18/1999	A
Ph I Bio M99-043 (75ug HGC)	NKACD082	06/30/1999	08/31/1999	09/30/1999	01/28/2000	A
Ph I Rising Multi HCG BID Doses	NKACP128	07/12/1999	09/10/1999	10/10/1999	03/15/2000	A
Ph III Osteoarthritis (Pivotal I)	NKACP302	12/01/1999	11/30/2000	01/14/2001	05/14/2001	A
Ph III Osteoarthritis (Pivotal II)	NKACD053	12/02/1999	12/01/2000	01/30/2001	05/30/2001	A
Ph III Osteoarthritis (Pivotal III)	NKACD070	12/03/1999	11/27/2000	12/27/2000	04/26/2001	A
Ph III Osteoarthritis Europe	NKACP323	12/05/1999	01/08/2001	02/07/2001	06/07/2001	A
Ph III Long Term Safety Europe	NKACD055	12/15/1999	07/01/2003	08/30/2003	12/18/2003	A
Ph III Long Term Safety	NKACP322	12/15/1999	07/01/2003	08/31/2003	12/29/2003	A
Human Metabolism (M98-986)	NKACP126	01/01/2000	04/30/2000	05/30/2000	08/28/2000	A
Ph I Pilot Bio Study (Ph III vs Comm Form)	NKACD089	01/10/2000	03/10/2000	04/09/2000	06/08/2000	A
Ph I Interaction # 1	NKACD021	01/10/2000	03/10/2000	04/09/2000	08/07/2000	A
Ph I Single Dose PK in Japanese	NKACD065	02/01/2000	04/01/2000	05/01/2000	08/29/2000	A
Ph I Cardiovascular Safety	NKACD078	02/01/2000	05/01/2000	05/31/2000	09/28/2000	A
Ph I PK in Elderly Subjects	NKACD064	02/15/2000	04/29/2000	05/29/2000	09/26/2000	A
Ph I PK Renal Impaired	NKACP109	02/15/2000	05/15/2000	06/14/2000	10/12/2000	A
Ph III Neuropathic Pain (Pivotal I)	NKACD052	03/01/2000	03/29/2001	04/28/2001	08/26/2001	A
Ph III Neuropathic Pain (Pivotal II)	NKACD018	03/08/2000	02/09/2001	03/11/2001	06/09/2001	A
Ph III Neuropathic Pain (Pivotal III)	NKACP301	03/15/2000	02/15/2001	04/16/2001	07/15/2001	A
Ph III Neuropathic Pain Europe	NKACD019	03/21/2000	01/26/2001	03/27/2001	06/25/2001	A
Ph I Interaction # 2	NKACD022	04/01/2000	05/31/2000	06/30/2000	09/28/2000	A
Ph I PK in Smokers	NKACD063	04/01/2000	06/30/2000	07/30/2000	11/27/2000	A

Page : 1

CONFIDENTIAL

ABBT 0019071

Activity Listing

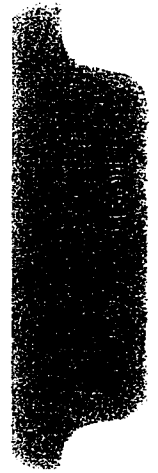
06/17/99

Sponsor	Clinical	Project	ABT-594	Indicatio	Pain (General)		
Version	Plan	Project N	G0 143010	Formulation	Oral Solid		
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code	
Ph I PK Hepatic Impaired	NKACP110	04/01/2000	06/30/2000	07/31/2000	10/29/2000	A	
Ph I Interaction # 3	NKACP112	05/01/2000	06/30/2000	07/30/2000	10/28/2000	A	
Ph II Cancer Pain	NKACD083	05/01/2000	02/01/2001	04/01/2001	07/01/2001	A	
Ph II Cancer Pain	NKACD084	05/07/2000	02/07/2001	03/15/2001	06/15/2001	A	
Ph I Interaction # 4	NKACP113	06/01/2000	07/31/2000	08/30/2000	11/28/2000	A	
Ph I Multi Dose PK in Japanese	NKACD080	06/01/2000	08/30/2000	09/29/2000	01/27/2001	A	
Ph I Interaction # 5	NKACD025	07/01/2000	08/30/2000	09/29/2000	12/28/2000	A	
Ph I Effect of Food in Japanese	NKACD066	08/01/2000	09/15/2000	10/15/2000	01/13/2001	A	
Ph I Interaction # 6	NKACD026	08/01/2000	09/30/2000	10/30/2000	01/28/2001	A	
Ph I Bio (Ph III Form vs Commercial Form)	NKACP130	10/01/2000	11/29/2000	12/30/2000	12/30/2000	A	
Ph III Osteoarthritis (Bridging) Japan	NKACD010	10/01/2000	09/06/2001	11/05/2001	03/05/2002	A	
Ph III Neuropathic (Bridging) Japan	NKACD081	11/01/2000	09/27/2001	10/27/2001	02/24/2002	A	
Ph IIIB Pricing Study U.S.	NKACD058	02/01/2001	10/29/2001	11/28/2001	03/28/2002	A	
Ph IIIB Pricing Study Australia	NKACD061	03/01/2001	11/26/2001	12/26/2001	04/25/2002	A	
Ph IIIB Pricing Study Canada	NKACD060	03/01/2001	11/26/2001	12/26/2001	04/25/2002	A	
Prepare ISS/ISE	NKACPY03	04/01/2001	09/15/2001	09/15/2001	09/15/2001	A	
Ph IIIB Pricing Study Europe	NKACD059	04/01/2001	12/27/2001	01/26/2002	05/26/2002	A	
NDA / EMEA Preparation	NKACPY01	07/01/2001	11/29/2001	11/29/2001	11/29/2001	A	
NDA / EMEA Filing	NKACPY08	12/01/2001	12/01/2001	12/01/2001	12/01/2001	A	
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Page : 2

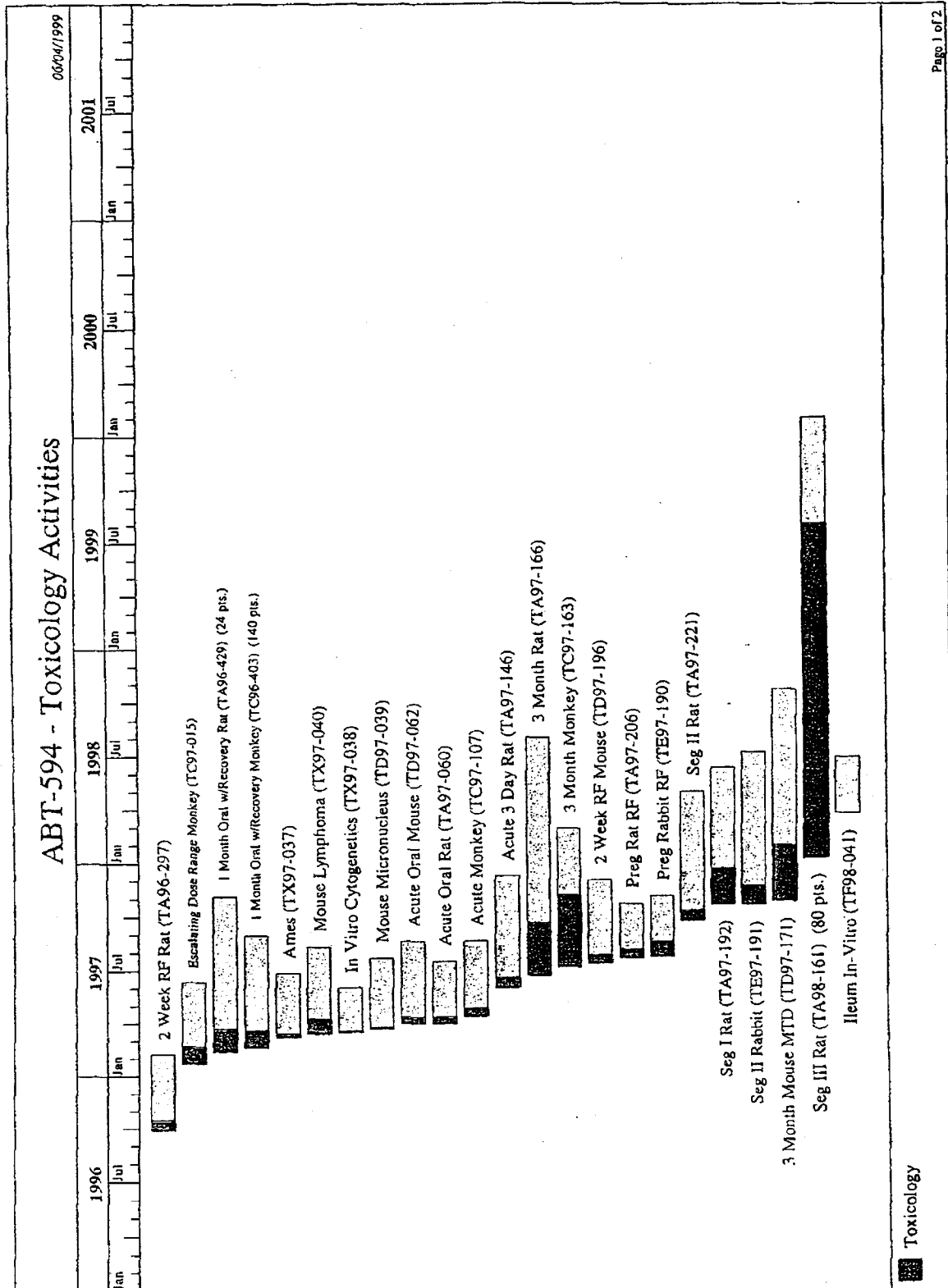
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ABBT 0019072



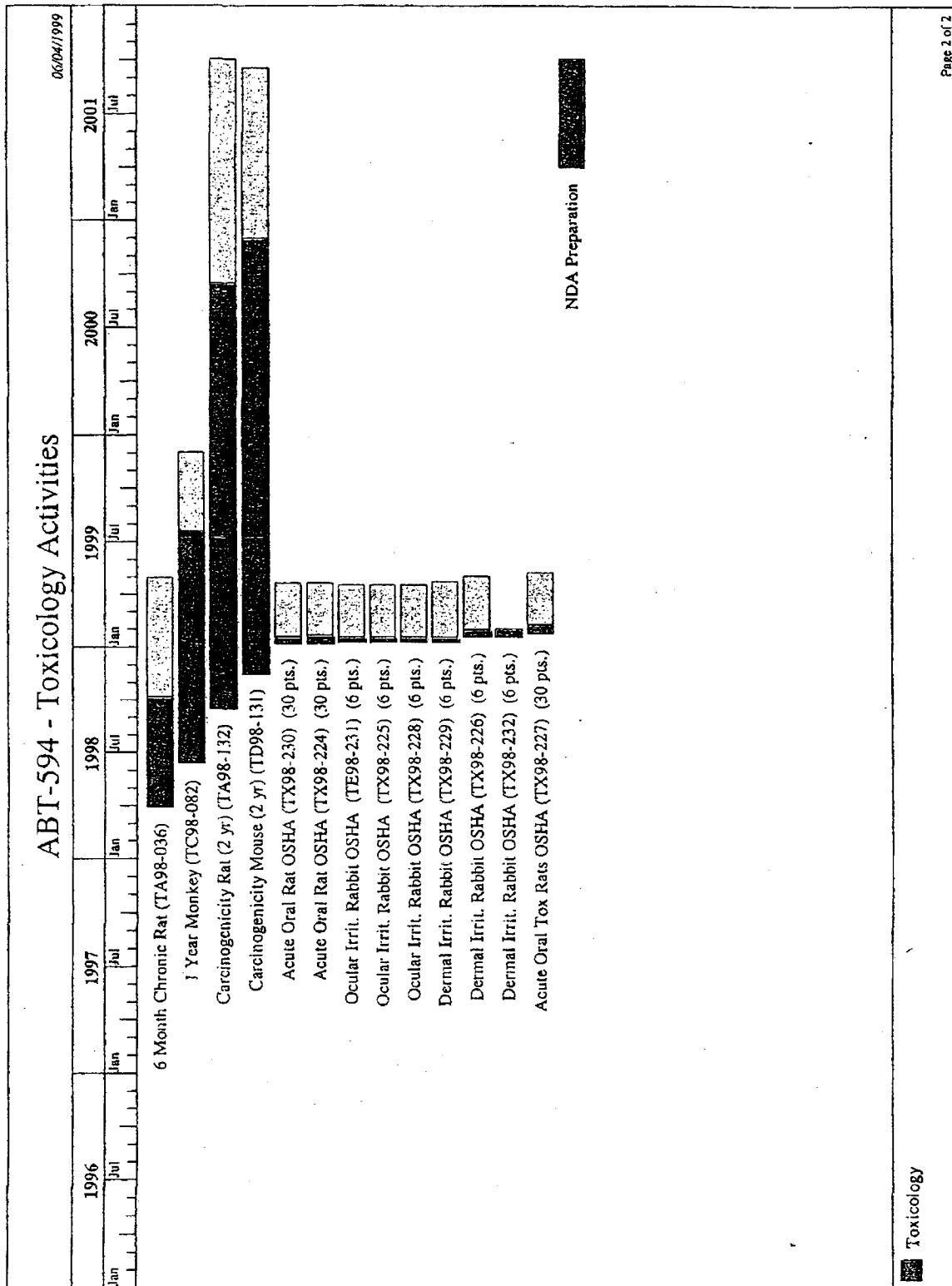
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ABBT 0019073



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ABBT 0019074



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ABBT 0019075

Activity Listing

06/17/99

Sponsor Toxicology		Project ABT-594		Indication Pain (General)			
Version	Plan	Project N	G0 143010		Formulation		Oral Solid
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
2 Week RF Rat (TA96-297)		NKATD013	09/26/1996	10/15/1996	10/15/1996	02/05/1997	C
Escalating Dose Range Monkey (TC97-015)		NKATD014	01/23/1997	02/22/1997	02/22/1997	06/12/1997	C
1 Month Oral w/Recovery Rat (TA96-429)		NKATST01	02/11/1997	03/25/1997	04/25/1997	11/05/1997	C
1 Month Oral w/Recovery Monkey (TC96-403)		NKATST04	02/18/1997	03/21/1997	03/21/1997	08/29/1997	C
Ames (TX97-037)		NKATTM06	03/10/1997	03/14/1997	05/01/1997	06/26/1997	C
Mouse Lymphoma (TX97-040)		NKATMU01	03/15/1997	04/12/1997	04/12/1997	08/11/1997	C
In Vitro Cytogenetics (TX97-038)		NKATTB02	03/17/1997	03/21/1997	06/01/1997	06/01/1997	C
Mouse Micronucleus (TD97-039)		NKATTM07	03/24/1997	03/28/1997	06/05/1997	07/23/1997	C
Acute Oral Rat (TA97-060)		NKATST02	04/01/1997	04/15/1997	04/15/1997	07/17/1997	C
Acute Oral Mouse (TD97-062)		NKATST03	04/01/1997	04/15/1997	04/15/1997	08/21/1997	C
Acute Monkey (TC97-107)		NKATTA01	04/15/1997	04/29/1997	04/29/1997	08/21/1997	C
Acute 3 Day Rat (TA97-146)		NKATD001	06/02/1997	06/19/1997	06/19/1997	12/08/1997	C
3 Month Rat (TA97-166)		NKATTB08	06/24/1997	09/23/1997	12/01/1997	08/03/1998	C
3 Month Monkey (TC97-163)		NKATTB09	07/09/1997	11/06/1997	12/16/1997	02/28/1998	C
2 Week RF Mouse (TD97-196)		NKATTS16	07/15/1997	07/30/1997	07/30/1997	11/30/1997	C
Preg Rat RF (TA97-206)		NKATTT10	07/24/1997	08/07/1997	08/07/1997	10/24/1997	C
Preg Rabbit RF (TE97-190)		NKATTT11	07/28/1997	08/20/1997	08/20/1997	11/05/1997	C
Seg II Rat (TA97-221)		NKATTT12	09/24/1997	10/14/1997	10/14/1997	05/01/1998	C
Seg II Rabbit (TE97-191)		NKATTT13	10/22/1997	11/21/1997	11/21/1997	07/07/1998	C
Seg I Rat (TA97-192)		NKATTT14	10/22/1997	12/22/1997	12/22/1997	06/10/1998	C
3 Month Mouse MTD (TD97-171)		NKATTC19	10/30/1997	01/30/1998	01/30/1998	10/23/1998	C
Seg III Rat (TA98-161)		NKATTT15	01/10/1998	08/04/1999	09/01/1999	01/31/2000	A
Ileum In-Vitro (TF98-041)		NKATXX34	03/24/1998	03/27/1998	03/27/1998	06/29/1998	C
6 Month Chronic Rat (TA98-036)		NKATCR33	03/31/1998	10/07/1998	11/06/1998	04/30/1999	C
1 Year Monkey (TC98-082)		NKATCR39	06/15/1998	07/22/1999	08/06/1999	11/30/1999	A
Carcinogenicity Rat (2 yr) (TA98-132)		NKATD010	09/17/1998	09/15/2000	10/15/2000	09/30/2001	A
Carcinogenicity Mouse (2 yr) (TD98-131)		NKATD011	11/15/1998	12/01/2000	02/01/2001	09/15/2001	A
Acute Oral Rat OSHA (TX98-230)		NKATF004	01/06/1999	01/20/1999	01/20/1999	04/20/1999	C
Acute Oral Rat OSHA (TX98-224)		NKATT007	01/07/1999	01/21/1999	01/21/1999	04/21/1999	C
Ocular Irrit. Rabbit OSHA (TX98-225)		NKATT008	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Ocular Irrit. Rabbit OSHA (TE98-231)		NKATT005	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Dermal Irrit. Rabbit OSHA (TX98-229)		NKATT003	01/11/1999	01/18/1999	01/18/1999	04/22/1999	C
Ocular Irrit. Rabbit OSHA (TX98-228)		NKATT002	01/11/1999	01/18/1999	01/18/1999	04/18/1999	C
Dermal Irrit. Rabbit OSHA (TX98-226)		NKATT009	01/18/1999	02/01/1999	02/01/1999	05/02/1999	A

Page : 1

CONFIDENTIAL

ABBT 0019076

Activity Listing

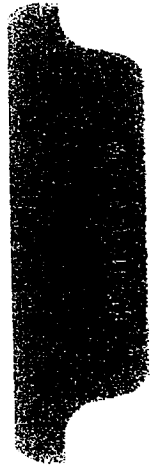
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Sponsor Toxicology		Project ABT-594		Indication Pain (General)			
Version Plan		Project N G0 143010		Formulation Oral Solid			
Description		AN Num	Stry Start	Stry End	DB End	Sum End	Status Code
Dermal Irrit. Rabbit OSHA (TX98-232)		NKATT006	01/18/1999	02/01/1999	02/01/1999	02/01/1999	C
Acute Oral Tox Rats OSHA (TX98-227)		NKATT010	01/25/1999	02/08/1999	02/08/1999	05/09/1999	A
NDA Preparation		NKATD012	04/01/2001	10/01/2001	10/01/2001	10/01/2001	A

Page : 2

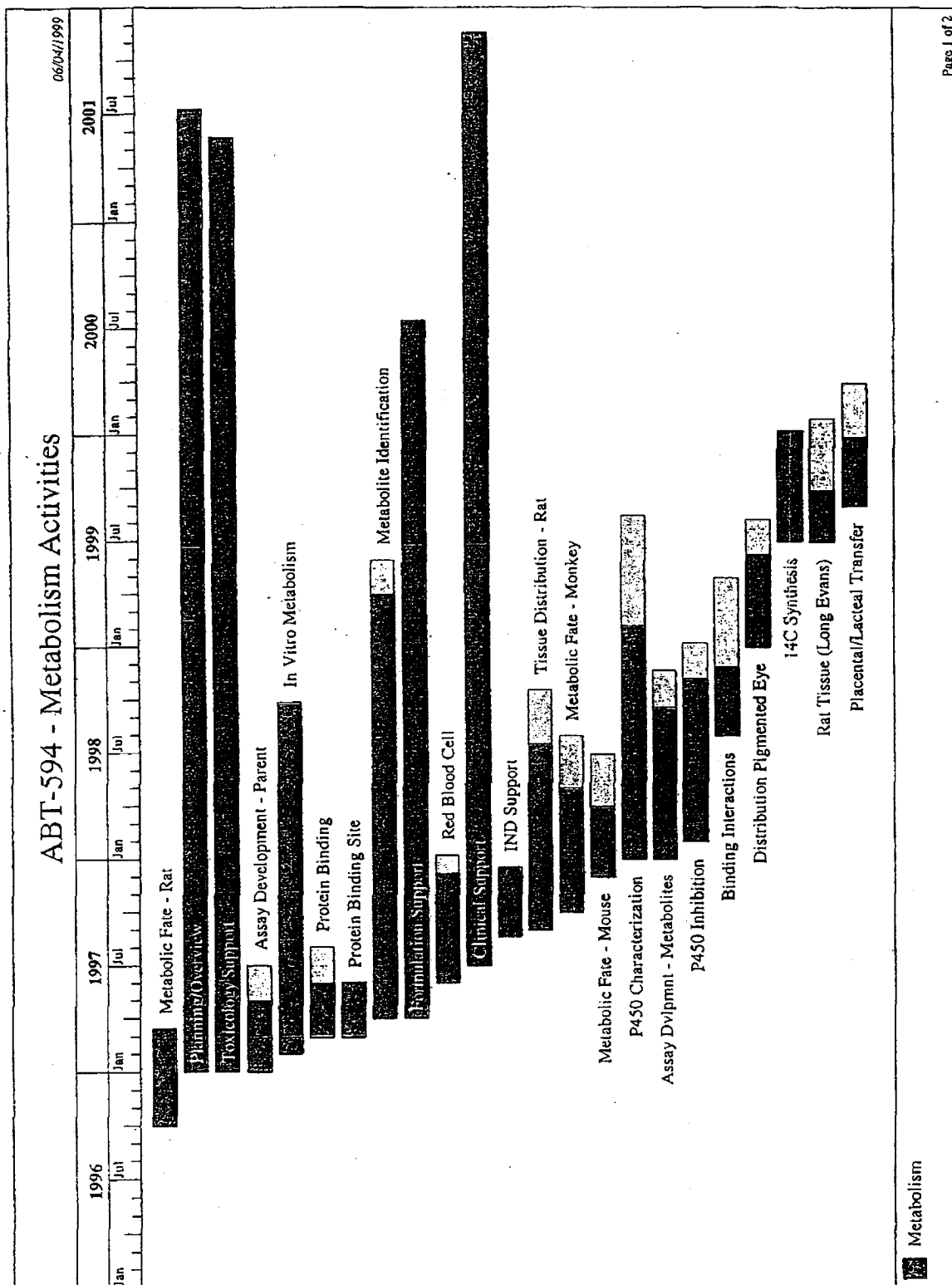
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ABBT 0019077



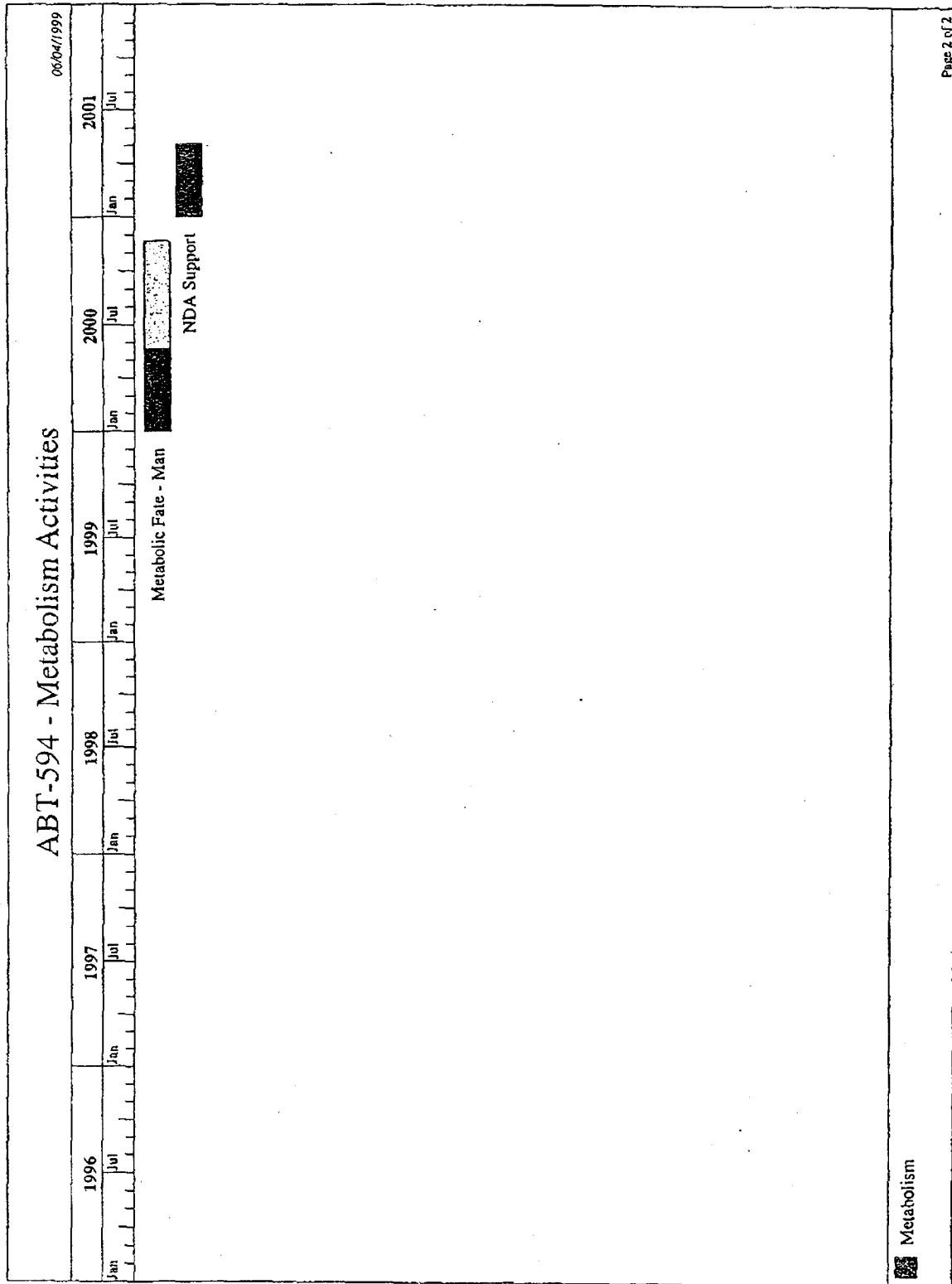
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ABBT 0019080

Activity Listing

06/17/99

Sponsor Metabolism		Project ABT-594		Indication Pain (General)			
Version	Plan	Project N	G0 143010	Formulation	Oral Solid		
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Metabolic Fate - Rat		NKAMMB03	10/01/1996	03/15/1997	03/15/1997	03/15/1997	C
Assay Development - Parent		NKAMMA02	01/01/1997	05/02/1997	07/01/1997	07/01/1997	C
Toxicology Support		NKAMD005	01/01/1997	05/20/2001	05/20/2001	05/20/2001	A
Planning/Overview		NKAMMS01	01/01/1997	07/09/2001	07/09/2001	07/09/2001	A
In Vitro Metabolism		NKAMMB14	02/01/1997	09/24/1998	09/24/1998	09/24/1998	C
Protein Binding Site		NKAMML01	03/01/1997	06/01/1997	06/01/1997	06/01/1997	C
Protein Binding		NKAMMB08	03/01/1997	06/01/1997	08/01/1997	08/01/1997	C
Metabolite Identification		NKAMMB06	04/01/1997	04/01/1999	04/01/1999	05/31/1999	A
Formulation Support		NKAMMS02	04/01/1997	07/14/2000	07/14/2000	07/14/2000	A
Red Blood Cell		NKAMMB01	06/01/1997	12/08/1997	12/08/1997	01/07/1998	C
Clinical Support		NKAMD006	07/01/1997	11/17/2001	11/17/2001	11/17/2001	A
IND Support		NKAMD002	08/19/1997	12/17/1997	12/17/1997	12/17/1997	C
Tissue Distribution - Rat		NKAMMB13	09/01/1997	07/18/1998	07/18/1998	10/16/1998	C
Metabolic Fate - Monkey		NKAMMB04	10/01/1997	05/01/1998	05/01/1998	07/30/1998	C
Metabolic Fate - Mouse		NKAMMB11	12/01/1997	04/01/1998	04/01/1998	06/30/1998	C
Assay Development - Metabolites		NKAMMA03	01/01/1998	09/18/1998	11/19/1998	11/19/1998	C
P450 Characterization		NKAMMB05	01/01/1998	02/05/1999	02/05/1999	08/14/1999	A
P450 Inhibition		NKAMMA01	02/01/1998	11/08/1998	11/08/1998	01/07/1999	C
Binding Interactions		NKAMMB09	08/01/1998	11/29/1998	12/29/1998	04/28/1999	C
Distribution Pigmented Eye		NKAMMB02	01/01/1999	06/10/1999	06/10/1999	08/09/1999	A
Rat Tissue (Long Evans)		NKAMD008	07/01/1999	09/29/1999	10/29/1999	01/27/2000	A
14C Synthesis		NKAMMS07	07/01/1999	01/07/2000	01/07/2000	01/07/2000	C
Placental/Lacteal Transfer		NKAMD007	09/01/1999	12/30/1999	12/30/1999	03/29/2000	A
Metabolic Fate - Man		NKAMMB07	01/02/2000	05/21/2000	08/21/2000	11/19/2000	A
NDA Support		NKAMD003	01/01/2001	05/01/2001	05/01/2001	05/01/2001	A

Page : 1

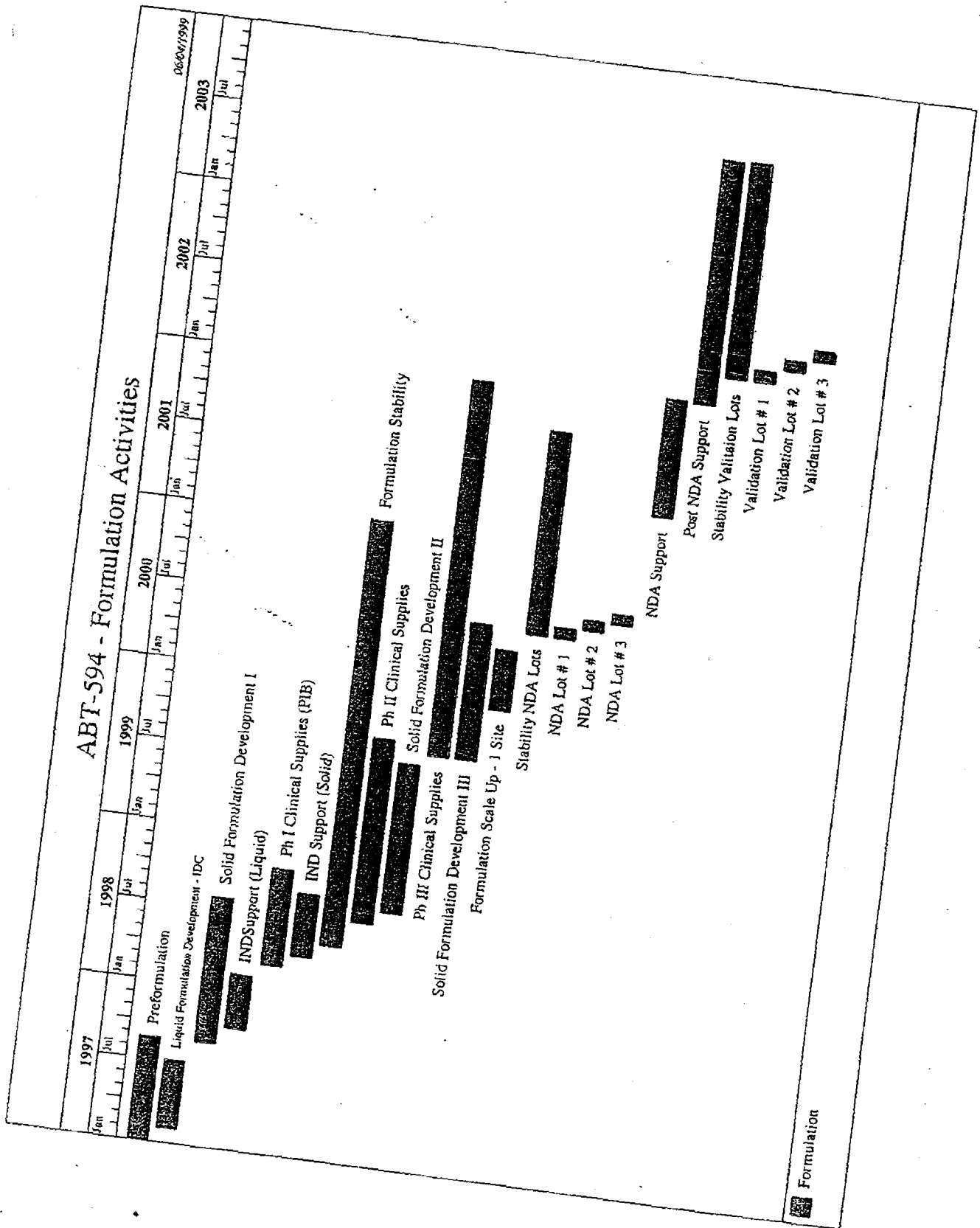
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ABBT 0019081



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ABBT 0019082



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ABBT 0019083

Activity Listing

06/17/99

Sponsor Formulation		Project ABT-594		Indicatio		Pain (General)	
Version	Plan	Project N	GO 143010		Formulation	Oral Solid	
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Preformulation		NKAWWD01	01/01/1997	08/19/1997	08/19/1997	08/19/1997	C
Liquid Formulation Development - IDC		NKAWD004	02/01/1997	07/01/1997	07/01/1997	07/01/1997	C
Solid Formulation Development I		NKAWWF02	08/22/1997	07/18/1998	07/18/1998	07/18/1998	C
INDSupport (Liquid)		NKAWD005	10/01/1997	01/29/1998	01/29/1998	01/29/1998	C
Ph I Clinical Supplies (PIB)		NKAWWG03	03/01/1998	10/07/1998	10/07/1998	10/07/1998	C
IND Support (Solid)		NKAWD009	04/01/1998	08/19/1998	08/19/1998	08/19/1998	C
Formulation Stability		NKAWD008	05/01/1998	01/01/2001	01/01/2001	01/01/2001	A
Ph II Clinical Supplies		NKAWWG05	07/01/1998	08/25/1999	08/25/1999	08/25/1999	A
Solid Formulation Development II		NKAWWF07	08/01/1998	07/07/1999	07/07/1999	07/07/1999	A
Solid Formulation Development III		NKAWWF04	08/01/1999	06/06/2000	06/06/2000	06/06/2000	A
Ph III Clinical Supplies		NKAWWG11	08/01/1999	12/08/2001	12/08/2001	12/08/2001	A
Formulation Scale Up - 1 Site		NKAWD010	12/01/1999	04/14/2000	04/14/2000	04/14/2000	A
Stability NDA Lots		NKAWD014	05/30/2000	09/12/2001	09/12/2001	09/12/2001	A
NDA Lot # 1		NKAWD011	06/01/2000	06/22/2000	06/22/2000	06/22/2000	A
NDA Lot # 2		NKAWD012	06/23/2000	07/14/2000	07/14/2000	07/14/2000	A
NDA Lot # 3		NKAWD013	07/15/2000	08/05/2000	08/05/2000	08/05/2000	A
NDA Support		NKAWD006	04/01/2001	12/22/2001	12/22/2001	12/22/2001	A
Post NDA Support		NKAWWS09	12/22/2001	06/25/2003	06/25/2003	06/25/2003	A
Stability Valitaion Lots		NKAWD018	02/28/2002	06/30/2003	06/30/2003	06/30/2003	A
Validation Lot # 1		NKAWD015	03/01/2002	03/22/2002	03/22/2002	03/22/2002	A
Validation Lot # 2		NKAWD016	04/01/2002	04/22/2002	04/22/2002	04/22/2002	A
Validation Lot # 3		NKAWD017	05/01/2002	05/22/2002	05/22/2002	05/22/2002	A

Page : 1

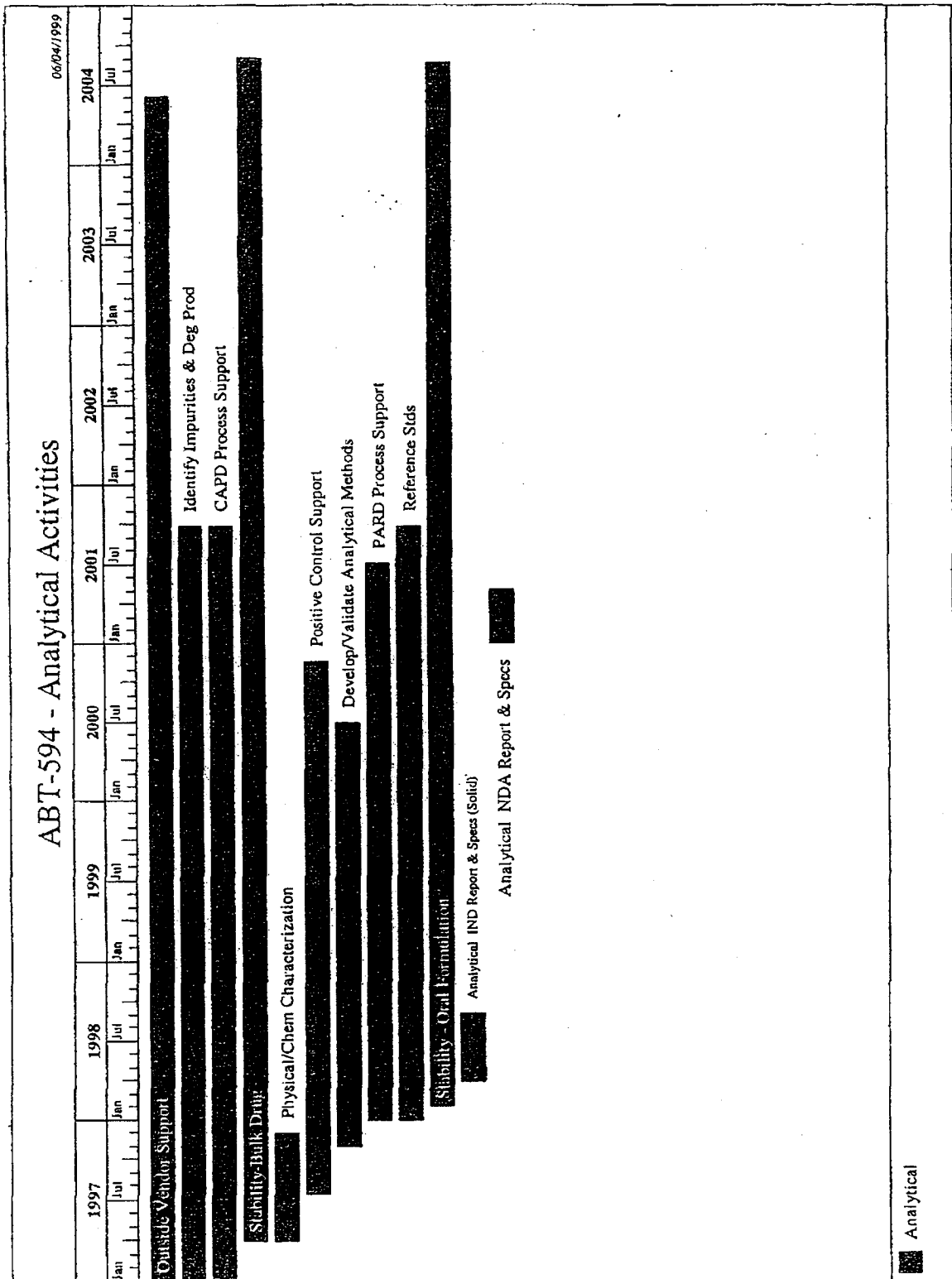
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ABBT 0019084



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ABBT 0019085



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ABBT 0019086

Activity Listing

06/17/99

Sponsor Analytical

Project ABT-594

Indication Pain (General)

Version Plan

Project N G0 143010

Formulation Oral Solid

Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Identify Impurities & Deg Prod	NKAVWC03	01/01/1997	09/27/2001	09/27/2001	09/27/2001	A
CAPD Process Support	NKAVD005	01/01/1997	09/27/2001	09/27/2001	09/27/2001	A
Outside Vendor Support	NKAVD006	01/01/1997	06/01/2004	06/01/2004	06/01/2004	A
Physical/Chem Characterization	NKAVWC07	04/01/1997	12/01/1997	12/01/1997	12/01/1997	C
Stability-Bulk Drug	NKAVD002	04/01/1997	08/30/2004	08/30/2004	08/30/2004	A
Positive Control Support	NKAVD010	07/15/1997	11/16/2000	11/16/2000	11/16/2000	A
Develop/Validate Analytical Methods	NKAVWC01	11/01/1997	06/28/2000	06/28/2000	06/28/2000	A
PARD Process Support	NKAVD009	01/01/1998	07/04/2001	07/04/2001	07/04/2001	A
Reference Stds	NKAVWC04	01/01/1998	09/27/2001	09/27/2001	09/27/2001	A
Stability - Oral Formulation	NKAVWC02	02/01/1998	08/18/2004	08/18/2004	08/18/2004	A
Analytical IND Report & Specs (Solid)	NKAVWS02	04/01/1998	09/01/1998	09/01/1998	09/01/1998	A
Analytical NDA Report & Specs	NKAVWS05	01/01/2001	05/01/2001	05/01/2001	05/01/2001	A

Page : 1

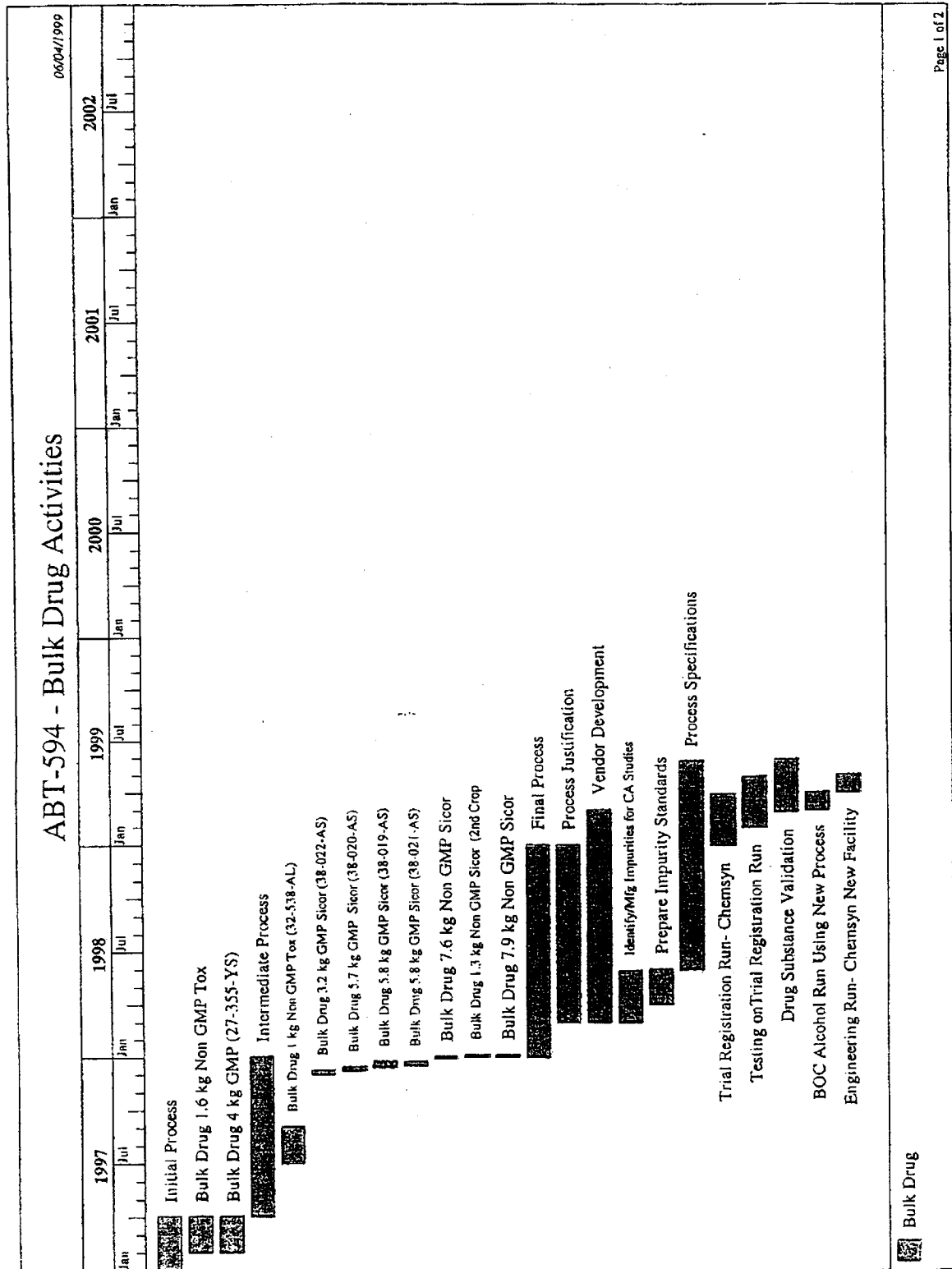
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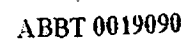
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ABBT 0019088



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ABBT 0019089



Activity Listing

06/17/99

Sponsor Bulk Drug		Project ABT-594		Indication Pain (General)		
Versio Plan		Project N GO 143010		Formulation Oral Solid		
Description	AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Initial Process	NKAUD030	01/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Bulk Drug 4 kg GMP (27-355-YS)	NKAUWG02	02/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Bulk Drug 1.6 kg Non GMP Tox	NKAUWG05	02/01/1997	04/01/1997	04/01/1997	04/01/1997	C
Intermediate Process	NKAUD031	04/01/1997	12/31/1997	12/31/1997	12/31/1997	C
Bulk Drug 1 kg Non GMP Tox (32-538-AL)	NKAUD012	07/01/1997	08/31/1997	08/31/1997	08/31/1997	C
Bulk Drug 3.2 kg GMP Sisor (38-022-AS)	NKAUWG08	12/01/1997	12/07/1997	12/07/1997	12/07/1997	C
Bulk Drug 5.7 kg GMP Sisor (38-020-AS)	NKAUWG09	12/08/1997	12/15/1997	12/15/1997	12/15/1997	C
Bulk Drug 5.8 kg GMP Sisor (38-019-AS)	NKAUD002	12/15/1997	12/22/1997	12/22/1997	12/22/1997	C
Bulk Drug 5.8 kg GMP Sisor (38-021-AS)	NKAUD003	12/17/1997	12/24/1997	12/24/1997	12/24/1997	C
Bulk Drug 7.6 kg Non GMP Sisor	NKAUD014	12/28/1997	01/02/1998	01/02/1998	01/02/1998	C
Bulk Drug 7.9 kg Non GMP Sisor	NKAUD015	12/31/1997	01/05/1998	01/05/1998	01/05/1998	C
Bulk Drug 1.3 kg Non GMP Sisor (2nd Crop)	NKAUD013	12/31/1997	01/05/1998	01/05/1998	01/05/1998	C
Final Process	NKAUD032	01/01/1998	12/31/1998	12/31/1998	12/31/1998	C
Identify/Mfg Impurities for CA Studies	NKAUD021	03/02/1998	05/29/1998	05/29/1998	05/29/1998	C
Process Justification	NKAUD023	03/02/1998	12/31/1998	12/31/1998	12/31/1998	C
Vendor Development	NKAUD020	03/02/1998	03/02/1999	03/02/1999	03/02/1999	C
Prepare Impurity Standards	NKAUD022	04/01/1998	06/03/1998	06/03/1998	06/03/1998	C
Process Specifications	NKAUD024	06/01/1998	05/27/1999	05/27/1999	05/27/1999	C
Trial Registration Run- Chemsyn	NKAUD025	01/01/1999	03/31/1999	03/31/1999	03/31/1999	C
Testing on Trial Registration Run	NKAUD026	02/01/1999	04/30/1999	04/30/1999	04/30/1999	C
Drug Substance Validation	NKAUD029	03/01/1999	05/30/1999	05/30/1999	05/30/1999	C
BOC Alcohol Run Using New Process	NKAUD034	03/02/1999	04/01/1999	04/01/1999	04/01/1999	C
Engineering Run- Chemsyn New Facility	NKAUD033	04/02/1999	05/02/1999	05/02/1999	05/02/1999	A
Bulk Drug GMP (MFG LOT)	NKAUD016	04/02/1999	05/02/1999	05/02/1999	05/02/1999	C
Registration Runs for Bulk @ Chemsyn	NKAUD027	07/01/1999	10/15/1999	10/15/1999	10/15/1999	A
Registration Run for BOC Alcohol @ Regis	NKAUD035	07/01/1999	09/29/1999	09/29/1999	09/29/1999	A
Testing on Registration Runs	NKAUD028	07/01/1999	11/30/1999	11/30/1999	11/30/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #1)	NKAUD017	08/01/1999	08/22/1999	08/22/1999	08/22/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #2)	NKAUD019	09/01/1999	09/22/1999	09/22/1999	09/22/1999	A
Bulk Drug 5 Kg GMP (NDA Lot #3)	NKAUD018	10/01/1999	10/22/1999	10/22/1999	10/22/1999	A
Bulk Drug 5 Kg GMP (Validation #1)	NKAUD036	10/01/2001	10/22/2001	10/22/2001	10/22/2001	A
Validation Runs	NKAUD040	10/01/2001	01/01/2002	01/01/2002	01/01/2002	A
Bulk Drug 5 Kg GMP (Validation #2)	NKAUD037	11/01/2001	11/22/2001	11/22/2001	11/22/2001	A
Bulk Drug 5 Kg GMP (Validation #3)	NKAUD038	12/01/2001	12/22/2001	12/22/2001	12/22/2001	A

Page : 1

CONFIDENTIAL

ABBT 0019091

Activity Listing

06/17/99

<i>Sponsor</i>	Bulk Drug	<i>Project</i>	ABT-594	<i>Indicatio</i>	Pain (General)	
<i>Versio</i>	Plan	<i>Project N</i>	GO 143010	<i>Formulation</i>	Oral Solid	
<i>Description</i>	<i>AN Num</i>	<i>Sty Start</i>	<i>Sty End</i>	<i>DB End</i>	<i>Sum End</i>	<i>Status Code</i>
Bulk Drug 5 Kg GMP (Validation #4)	NKAUD039	01/01/2002	01/22/2002	01/22/2002	01/22/2002	A

Page: 2

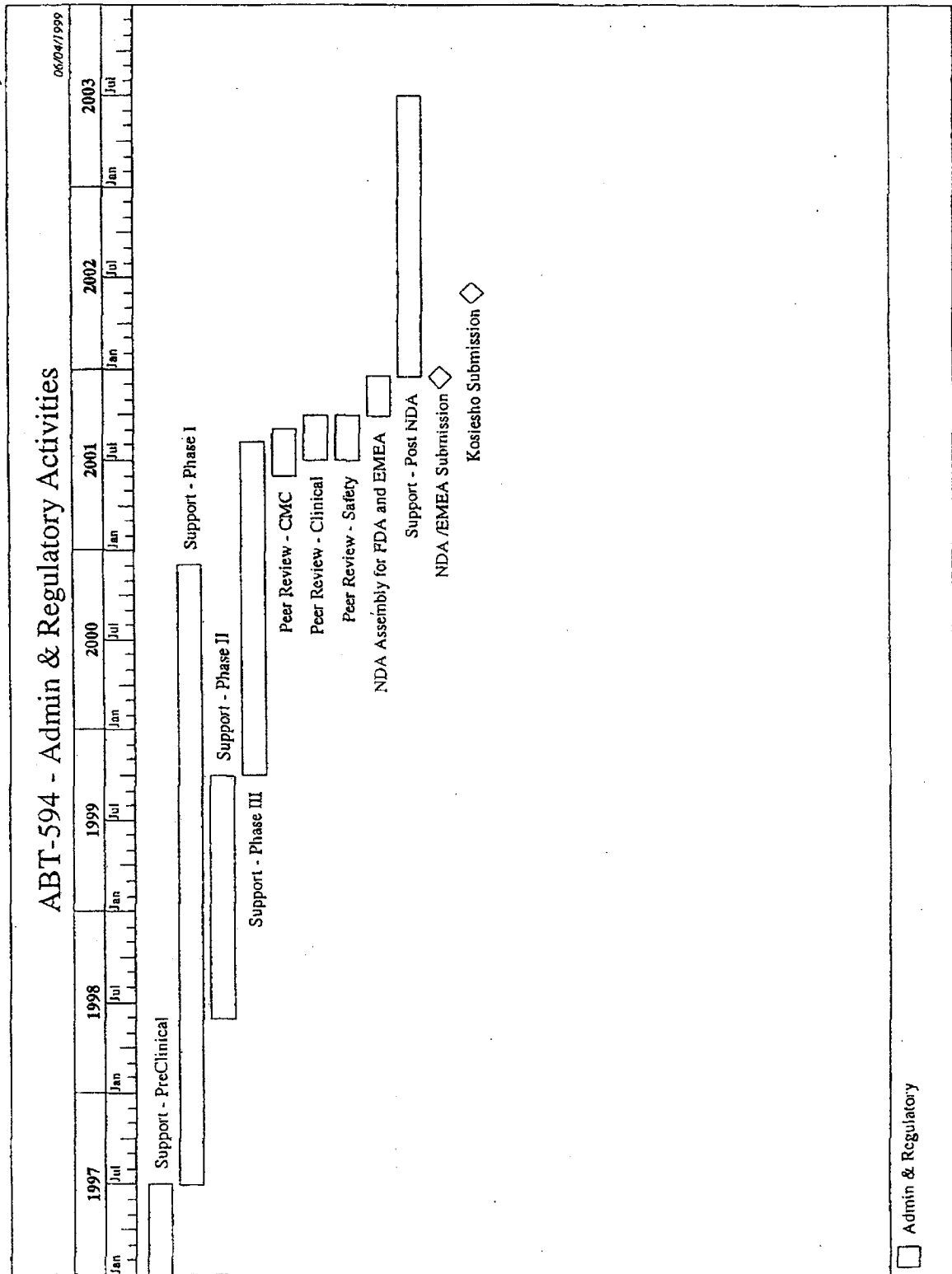
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ABBT 0019092



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ABBT 0019093



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ABBT 0019094

Activity Listing

06/17/99

Sponsor Admin & Regulatory		Project ABT-594		Indicatio Pain (General)			
Version	Plan	Project N	GO 143010	Formulation	Oral Solid		
Description		AN Num	Sty Start	Sty End	DB End	Sum End	Status Code
Support - PreClinical		NKAZPS06	01/01/1997	07/01/1997	07/01/1997	07/01/1997	C
Support - Phase I		NKAZPS07	07/01/1997	12/01/2000	12/01/2000	12/01/2000	A
Support - Phase II		NKAZPS08	06/01/1998	09/30/1999	09/30/1999	09/30/1999	A
Support - Phase III		NKAZPS09	10/01/1999	08/06/2001	08/06/2001	08/06/2001	A
Peer Review - CMC		NKAZPS01	06/01/2001	08/31/2001	08/31/2001	08/31/2001	A
Peer Review - Safety		NKAZPS02	07/01/2001	10/01/2001	10/01/2001	10/01/2001	A
Peer Review - Clinical		NKAZPS03	07/01/2001	10/01/2001	10/01/2001	10/01/2001	A
NDA Assembly for FDA and EMEA		NKAZD003	10/01/2001	12/15/2001	12/15/2001	12/15/2001	A
NDA /EMEA Submission		NKAZD005	12/15/2001	12/15/2001	12/15/2001	12/15/2001	A
Support - Post NDA		NKAZPS10	12/15/2001	06/30/2003	06/30/2003	06/30/2003	A
Kosiesho Submission		NKAZD006	06/01/2002	06/01/2002	06/01/2002	06/01/2002	A

Page : 1

CONFIDENTIAL

ABBT 0019095

McCarthy Deposition Exhibit 10

P's Exhibit CB

ABT-594 Project Status Report

Marc/ '000

Business Rationale

Date: March, 2000
Franchise: Neuroscience
Venture: Analgesia

ABT #:
Trade & Generic Name:
Mechanism of Action:

Indications: Neuropathic Pain
Chronic Pain (publication only)

ABT-594
TBO, TBO
Cholinergic Channel Modulator (ChCM)

Development Cost

	PPCC/ODC 12/1995 (\$MM)	Plan as of 11/1998** (\$MM)	Plan as of 11/1999*** (\$MM)
Cost to NDA (Cost to Next GenCo (Phase II clinical efficacy) Cum. Cost through 1999 2000 Funding Request 2000 Plan (funded) Current Projection YTDAM	163 — — — — — —	185 45 — 71 — — —	215 16 31 21 15 15 1

***Assume Phase II GOING TO 95%; NDA filing 12/01
***Assume Phase III GOING TO 95%; NDA filing 5/03

Product Profile

Attribute	Date Defined	Probability	Confirm Status	Share Impact
Not scheduled	12/1995	High	100%	High
Chronic nociceptive pain efficacy	10/1999	Medium	2Q01	High
Neuropathic pain claim	6/1999	Medium	2Q01	High
General pain claim	12/1995	N/A	N/A	High
No tolerance/dependence or withdrawal	9/1998	Medium	1Q03	High
Moderate to moderately severe pain	9/1998	High	2Q01	High
Very low abnormal LFTs	6/1999	Medium	2Q01	High
Low emesis/vomiting at effective dose	9/1998	Medium	2Q01/Q03	High
Other safety OK	9/1998	High	2Q01/Q03	High
No differential efficacy (including users vs non users)	9/1998	Medium	2Q01/Q03	Medium
No differential side effect profile (including users vs non users)	9/1998	N/A	N/A	Medium
No transition of cravings in ex-addictive users	9/1998	Low	4Q01	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for neuropathic pain	8/1999	High	2Q01	High
RID dosing	8/1999	High	1Q03	High
No major drug interactions	12/1995	High	1Q03	High
Tolerability of 2.5 days duration required in minimize nausea and vomiting at effective dose.	8/1999	Medium	1Q03	High

*Probability Key:
High = 70-100%
Medium = 30-69%
Low = 0-29%

	PPCC/ODC 12/1995**	Plan as of 6/1998*	Current Revised 10/1999**
Patent Status:	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
NDA Filing	12/1999 (acute)	12/2001	5/2003
ex-U.S. Filings:	6/2001 (chronic)	12/2001 - Eur	Update Pending
Projected U.S. Launch:	Same as above - Eur	12/2003 - Jpn	5/2004
Projected ex-U.S. Launches:	12/2002 (chronic)	6/2003	Update Pending
Peak TRx Share, U.S.:	Same as above - Eur	12/2003 - Eur	Update Pending
	N/A - Jpn	9/20/2004 - Jpn	20%
	6.6% (patients)	5% (Rx)	(Neuropathic pain)
			10%
			(Persistent Chronic Pain)
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	5% patients
Peak Sales, U.S.:	\$285	\$615	\$357
Peak Sales, ex-U.S.:	\$308	\$310	Update Pending
After-Tax NPV @ 12.5% U.S.:	\$412	\$813	\$296
Pre-Tax NPV @ 15% ex-U.S.:	\$338	\$305	Update Pending
Avg daily dose	50 mg	200 mcg	150 µg
Target Drug Cost/Wg at Launch	\$2,500	\$2,500	\$2,500
SMM at Launch	94.8%	97.2%	98.6%

*Forecast based on general pain target indication

**Forecast based on neuropathic pain indication and published study in chronic pain

EXHIBIT
McCarthy
10
9-29-06 db

ABBT 0004401
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March 2000 ABT-594 Project Status Report

Project Overview

Description	Milestones PPCC/DDC 12/1996	Plan 6/1998	Plan 6/1999	Activity	PARD		
					Plan 6/1998	Plan 6/1999	Actual
PPCC Approval	12/1996	12/1996	12/1996	Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Start Phase I	6/1997	7/1997	7/1997	Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Go/No Go Clinical Safety	1/1998	4/1998	4/1998	Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Start Phase II	12/1997	7/1998	7/1998	Clinical Supplies (SEC) Shipped	10/1998	10/1998	10/1998
Go/No Go Clinical Efficacy	12/1998	6/1999	9/1999	(Osteoarthritis, Surgery, Neuropathy)			
Start Phase III	3/1999	8/1999	1/2000	Phase III Formulation (Tablet/HCC) for Bio Study	3/1999	3/1999	3/1999
File NDMEEA	12/1999 (acute) 6/2001 (chronic)	12/2001 (acute) 6/2003 (chronic)	12/2001	Phase III Clinical Supplies Manufactured	9/1999	9/1999	TBD
Regulatory approval	6/2001 (acute)	12/2001 (acute)	6/2003	NDA Lots (3) Completed	6/2000	6/2000	TBD
	12/2002 (chronic)	6/2003 (chronic)		Completion of 1 Year Stability for NDA	7/2001	7/2001	TBD
				Formulation Peer Review	10/2001	10/2001	TBD
				* Performed by IUC			

CAPD

Drug Substance Source/Lot #	KG Orig/Revised	Plan 6/1999	Actual Date	Actual/ Projected Cost/Kg*	Toxicology		
					Plan 1998 Start	Plan 1999 Start	Report Completed
D-45L	0.5 KG	12/1996	12/1996	\$ 200,000	2/1997	2/1997	8/1997
CAPD	6.7 KG	3/1997	3/1997	\$ 175,000	3/1997	3/1997	8/1997
SICOR	20.4 KG	12/1997	12/1997	\$ 40,000	2/1997	2/1997	11/1997
SICOR/CAPD	2.5 KG	7/1998	7/1998	\$ 40,000	7/1997	7/1997	8/1998
CHEMSYN PILOT LOT	2.00 KG	5/1999	TBD	\$ 29,700	10/1997	10/1997	10/1998
CHEMSYN MFG LOT	10.0 KG	10/1999	TBD	\$ 29,700	10/1997	10/1997	7/1998
CHEMSYN NDA LOT #1	10.0 KG	10/1999	TBD	\$ 29,700	1/1999	1/1999	Ongoing
CHEMSYN NDA LOT #2	10.0 KG	10/1999	TBD	\$ 29,700	3/1998	3/1998	7/1999
CHEMSYN NDA LOT #3	10.0 KG	10/1999	TBD	\$ 29,700	6/1998	6/1998	Ongoing
					12/1998	9/1998	Ongoing
					12/1998	11/1998	Ongoing

*Target cost of drug substance at launch is \$2,500/kg (Finished Product)

ABBT 0004402
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March 2000
ABT-594 Project Status Report
11/99 LRP

Development Program Costs (\$MM)

	Cumulative Thru 1998	1999 AGU	Cumulative Thru 1999	Plan 2000	Cumulative Thru 2000	Plan 2001	Cumulative to NDA Filing
Clinical Program	13.8	9.1	22.9	8.4	31.3	82.8	157.1
CMC (PARD & CAPD)	8.1	4.9	13.0	2.8	15.8	4.4	27.6
Drug Safety	5.4	3.3	8.7	3.1	11.8	4.3	18.3
Other Support Costs	3.3	2.6	5.9	0.7	6.6	2.9	12.2
Total	30.6	19.9	50.5	15.0	65.5	94.4	215.2

FILE NDA = 5/2003

CLINICAL PROGRAM = GRANTS, DATA MGT/STATS, VENTURE MANAGEMENT, DRUG SAFETY

ABBT 0004103
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March 2000
ABT-594 Project Status Report

Progress Gauges Previous Month (February)	Target Date	Status
Sign-off protocols M99-114 and M99-115	2/4/00	Completed
Complete Investigator Brochure Update	2/4/00	Completed
Send Regulatory Packet to potential investigators for M99-114/M99-115	2/15/00	Completed
Approve 75 µg HGC and Placebo Phase 2 clinical supplies	2/15/00	Completed
Resolve specifications on mesylate	2/15/00	Completed
M99-114 (Neuropathic Pain) investigator meeting	2/25/00	Completed
Complete all pre-study visits M99-114/M99-115	2/25/00	Completed
Current Month (March)	Target Date	Status
M99-115 Investigator Meeting	3/4/00	
Begin initiation visits M99-114 / M99-115	3/15/00	
Complete 80% M99-114 Investigator Grants	3/24/00	
Complete 50% M99-115 Investigator Grants	3/24/00	
Complete 70% IRB Approvals for M99-114 Study Sites	3/24/00	
Complete 90% IRB Approvals for M99-115 Study Sites	3/24/00	
Ship study drug M99-114 / M99-115	3/29/00	

	PPCC 12/1996	Plan as of 6/1997	Plan as of 8/1998	Plan as of 10/1999
NDA Filing	12/1999 (acute) 07/2001 (chronic)	06/2000 (acute) 12/2001 (chronic)	12/2001 (combined)	5/2003 Neuropathic Pain, Chronic Pain (Publication only)
NDA Approval	06/2001 (acute) 12/2002 (chronic)	12/2001 (acute) 06/2003 (chronic)	06/2003 (combined)	5/2004 Neuropathic Pain, Chronic Pain (Publication only)

ABBT 0004404
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Marc 2000
ABT-594 Project Status Report

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Vendor	Project Milestone (GO/NO GO) was achieved on target.	Data from Phase II studies were presented at Portfolio Review (October 6, 1999). The project team recommendations were supported: <ul style="list-style-type: none"> Establish a maximum tolerated dose of the hard gelatin capsule (HGC) dosage form. Continue with Phase IIB at higher doses.
NPD	If ABT-594 is scheduled, the NPV is significantly reduced.	An expert advisory meeting took place 11/98. The advisors felt it was unlikely that ABT-594 would be scheduled and recommended that we conduct several preclinical/clinical studies when a GO decision is made for Phase III development.
PARD	75 µg HGC will be made for Phase IIB. Higher capsule strengths may be required.	Hard gelatin capsule (HGC) has been chosen as the Phase IIB/III formulation. In order to start Phase III in 3Q/2001, Phase III formulation process optimization needs to start 4Q 2000. Some bias noted in assay method. Detailed investigation ongoing to determine cause. Puerto Rico facility being made ready for production.
CAPD	We are at risk for possible increases in the cost of drug substance because we are dependent on other vendors to manufacture ABT-594 drug substance. Toxicology has recommended an impurity limit for mesylate needs to be set below the level of detection (LOD 0.002 & LOQ 0.005). A recrystallization procedure will be needed. Additional process work may be needed depending upon the outcome of the recrystallization process.	Abbott cannot manufacture highly potent compounds. CAPD has identified several potential vendors for the drug substance: Sicor, Chemsyn and Calaytica. Chemsyn has been selected as the manufacturer of the bulk drug substance. Three registration lots totaling 16 Kg have been completed at Chemsyn. A meeting to discuss setting the mesylate impurity limit was held on September 30, 1999. A specification set below the current limit of detection was advised by toxicology. CMC technical committee meeting held 1/6/00 to discuss mesylate specifications. Recommendations made: Mesylate specification at target: not more than 0.005%. Incorporated into Standard Control Procedure. Development of a recrystallization process of the current method has started. This is planned to be incorporated into the process for the registration lots. All 3 registration lots recrystallized. All below 0.005% mesylate. Alternate chemical synthesis to eliminate mesylate going well in lab. Determination to proceed with alternate synthesis to be added to CMC Technical Committee docket for end of April.
Toxicology	6 month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long term toxicology studies. If higher doses (>75 µg BID) are used in future clinical studies and registration purposes, another rat CA study using higher doses will need to be initiated.	No adenomas have been found in the study. Early deaths in the 2 year carcinogenicity study will be closely monitored. No further studies are recommended at this time. Following dose selection, additional rat CA studies will be initiated in 2000. Justification for dose selection in rat CA studies submitted to FDA 1/25/00. No response as yet from FDA regarding dose selection.

ABT 0004405
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February 2000
ABT-594 Project Status Report (Continued)

Area	Issue/Decision/Event	Progress
Patent	Follow-on compounds discovered using human recombinant nAChR proprietary technology present increased risk.	<p>Efforts initiated in March, 1999 to negotiate with SIBIA for the rights to use the human recombinant neuronal nicotinic receptor constructs as a screening tool have been terminated due to subsequent exclusive licensing for a period of three years of this technology by SIBIA to Eli Lilly. Merck has subsequently assumed control of SIBIA. To minimize risk associated with the use of the human clonal cell lines, Abbott has initiated a strategy of using only human subtype combinations not currently covered by existing issued US patents, and to concurrently pursue the cloning and expression of non-human nAChRs that fall outside the scope of SIBIA's patent estate.</p> <p>Cloning of the ferret $\alpha 4$, $\alpha 3$, $\beta 2$, and $\beta 4$ subunits is proceeding. Current results suggest that the homology between ferret and human is higher than between rat and human, and is >90% in the highly conserved membrane spanning and ligand binding domains, but that overall homology will likely be less than 90%. It is anticipated that the first of the ferret nAChR subtypes ($\alpha 4\beta 2$) will be completed by 1Q00.</p> <p>To expand compound libraries and identify novel structural classes, Abbott has partnered with Neurosearch..</p> <p>First joint research council meeting with Neurosearch held 1/31-2/1/00. One compound identified that appears to be 4-fold better based on Chung model vs emesis model.</p> <p>Evaluating potential anti-depressant compound from this class.</p> <p>Three to five compounds to be chosen as follow-on to ABT-594 by May 2000. Of these 3-5 compounds, one will be chosen in July/Aug for Q4 2000 DDC.</p>

ABT 0004406
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Marc 1000 ABT-594 Project Status Report

Business Rationale

Date: March, 2000
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594
Trade & Generic Name: TBD, TBO
Mechanism of Action: Cholinergic Channel Modulator (ChCM)

Indications: Neuropathic Pain
Chronic Pain (publication only)

Development Cost

PPCC/DOC	12/1996	Plan as of 11/1999**	Plan as of 11/1999***
(\$MM)	11/1998** (\$MM)	(\$MM)	(\$MM)
Cost to TADA	163	188	215
Cost to Heat Condo Co	—	45	16
(Phase II clinical efficacy)	—	—	—
Current Cost through 1999	—	—	51
2000 Funding Request	—	71	21
2000 Plan (funded)	—	—	15
Current Projection	—	—	15
Y10A M	—	—	1

** Based on 4D Model
*** Assume Phase II GOHNO GO 989; NDA filing 2001
**** Assume Phase IIb GOHNO GO 201; NDA filing 2001

Product Profile

Attribute	Date Defined	Probability	Confirm Status	Share Impact
Not scheduled	12/1996	High	100%	High
Chronic nociceptive pain efficacy	10/1999	Medium	200%	High
Neuropathic pain claim	6/1999	Medium	200%	High
General pain claim	12/1998	N/A	N/A	High
Moderate to moderately severe pain	9/1998	Medium	100%	High
No tolerance dependence or withdrawal	9/1998	High	200%	High
Very low abdominal PTs	6/1999	Medium	200%	High
Low nausea/vomiting at effective dose	9/1998	Medium	200%/100%	High
Other safety OK	9/1998	High	200%/100%	High
No differential efficacy (intrathecal users vs oral users)	9/1998	Medium	200%/100%	Medium
No differential side effect profile (intrathecal users vs oral users)	9/1998	N/A	N/A	Medium
No reduction of cravings in ex-micaine users	6/1999	Low	400%	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	High	200%	High
No major drug interactions	12/1996	High	100%	Medium
Titration of 7.5 days duration required to minimize nausea and vomiting at effective dose	9/1999	Medium	100%	High

* Probability Key
High = 70-100%
Medium = 30-65%
Low = 0-25%

Market Forecast

PPCC/DOC	12/1996	Plan as of 6/1998*	Plan as of 10/2016 (est.)	Current Revised 10/1999**
Patent Status:	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)	10/2016 (est.)
NDA Filing:	12/1999 (acute)	12/2001	12/2001	5/2003
ex-U.S. Filings:	Same as above - Eur	12/2001 - Eur	12/2001 - Eur	Update Pending
Projected U.S. Launch:	12/2001 (acute)	6/2003	6/2003	5/2004
Projected ex-U.S. Launches:	Same as above - Eur	12/2003 - Eur	12/2003 - Eur	Update Pending
Peak TRx Share, U.S.:	6.6% (patients)	5% (Rx)	5% (Rx)	20% (Neuropathic pain)
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	5% (patients)	10% (Persistent Chronic Pain)
Peak Sales, U.S. (\$MM)	\$285	\$518	\$518	\$367
Peak Sales, ex-U.S. (\$MM)	\$308	\$310	\$310	Update Pending
After-Tax NPV @ 12.5%, U.S. (\$MM)	\$412	\$813	\$813	\$296
Pre-Tax NPV @ 15%, ex-U.S. (\$MM)	\$338	\$305	\$305	Update Pending
Avg daily dose	50 mg	200 mcg	200 mcg	150 mcg
Target Drug Cost/kg at Launch	\$2,500	\$2,500	\$2,500	\$2,500
MM at Launch	94.8%	97.2%	97.2%	98.6%

* Forecast based on general pain target indication

** Forecast based on neuropathic pain indication and published study in chronic pain

ABT 0004407
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March 2000 ABT-594 Project Status Report

Project Overview

Milestones	Description	PPCC/ODC			PARD		
		12/1996	Plan 6/1998	Plan 12/1996	Plan 6/1998	Plan 6/1999	Actual 7/1997
PPCC Approval		12/1996	12/1996	12/1996	6/1997	7/1997	7/1997
Start Phase I		6/1997	7/1997	7/1997	7/1998	7/1998	7/1998
Go/No Go Clinical Safety		1/1998	4/1998	4/1998	7/1998	7/1998	7/1998
Start Phase II		12/1997	7/1998	7/1998	10/1998	10/1998	10/1998
Go/No Go Clinical Efficacy		12/1998	9/1999	9/1999	3/1999	3/1999	3/1999
Start Phase III		3/1999	8/1999	8/1999	9/1999	9/1999	9/1999
File NDA/IND		12/1999 (acute)	12/2001 (acute)	12/2001 (acute)	6/2000	6/2000	6/2000
Regulatory approval		6/2001 (chronic)	6/2003 (chronic)	6/2003 (chronic)	7/2001	7/2001	7/2001
		12/2002 (chronic)	6/2003 (chronic)	6/2003 (chronic)	10/2001	10/2001	10/2001

CAPD

Drug Substance Source/Lot #	KG	Orig/Revised	Plan 6/1999	Actual Date	Actual Projected Cost/UG*
D-45L	0.5 KG		12/1996	12/1996	\$ 200,000
CAPD	6.7 KG		3/1997	3/1997	\$ 175,000
SICOR	20.4 KG		12/1997	12/1997	\$ 40,000
SICOR/CAPD	2.5 KG		7/1998	7/1998	\$ 40,000
CHEMSYN PILOT LOT	2.00 KG		5/1999	TBD	\$ 29,700
CHEMSYN MFG LOT	10.0 KG		10/1999	TBD	\$ 29,700
CHEMSYN NDA LOT #1	10.0 KG		10/1999	TBD	\$ 29,700
CHEMSYN NDA LOT #2	10.0 KG		10/1999	TBD	\$ 29,700
CHEMSYN NDA LOT #3	10.0 KG		10/1999	TBD	\$ 29,700

*Target cost of drug substance at launch is \$2,500/kg [Finished Product]

Toxicology

Toxicology Activity	Plan 1998 Start	Plan 1998 Start	Actual Start Date	Report Completed
Gene Toxicology	2/1997	2/1997	9/1996	8/1997
Acute Studies	3/1997	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	—	1/1999	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	6/1998	Ongoing
Carcinogenicity (2 yr) Rat	12/1998	9/1998	9/1998	Ongoing
Carcinogenicity (2 yr) Mouse	12/1998	11/1998	11/1998	Ongoing

ABT 0004408
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March 2000
ABT-594 Project Status Report
11/99 LRP

<u>Development Program Costs (\$MM)</u>						
	Cumulative Thru 1998	1999 AGU	Cumulative Thru 1999	Plan 2000	Cumulative Thru 2000	Plan 2001
Clinical Program	13.8	9.1	22.9	8.4	31.3	82.8
CMC (PAR & CAPD)	8.1	4.9	13.0	2.8	15.8	4.4
Drug Safety	5.4	3.3	8.7	3.1	11.8	4.3
Other Support Costs	3.3	2.6	5.9	0.7	6.6	2.9
Total	30.6	19.9	50.5	15.0	65.5	94.4
						215.2

FILE NDA = 5/2003

CLINICAL PROGRAM = GRANTS, DATA MGT/STATS, VENTURE MANAGEMENT, DRUG SAFETY

ABT 0004409
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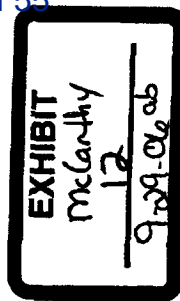
McCarthy Deposition Exhibit 12

P's Exhibit HN

Program Advancements

- ABT-594 Clinical progress:
 - Proof of principle in neuropathic pain and pain associated with osteoarthritis
 - Re-evaluation of maximum tolerated dose
- Established research collaboration with NeuroSearch
 - Access to human recombinant nAChRs
 - New proprietary chemical series
- Identification of backup series to ABT-594
- New therapeutic indications
 - Leads for novel antidepressant
 - Leads for novel antipsychotic

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ABBT 0021817



Cholinergic Channel Modulation

May, 2000

ABT-594: Clinical Advancements

- Phase II proof-of-principle for cholinergic channel modulation in acute analgesia (Molar extraction)
- Indications of efficacy in pain associated with osteoarthritis and neuropathic pain
- Statistically significant effects in diabetic neuropathy subset
- Tolerability much better than anticipated

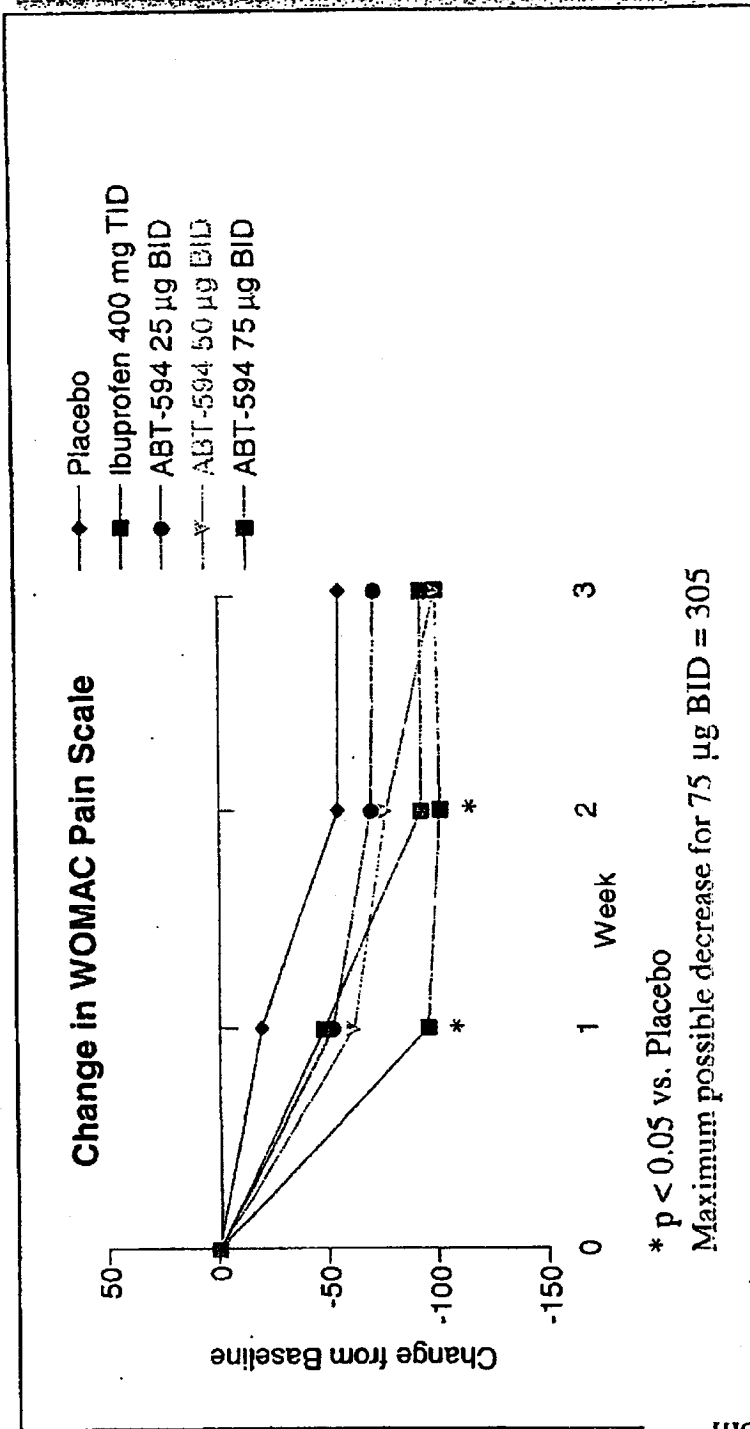
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ABBT 0021818

May, 2000

Cholinergic Channel Modulation

Pain Associated with Osteoarthritis



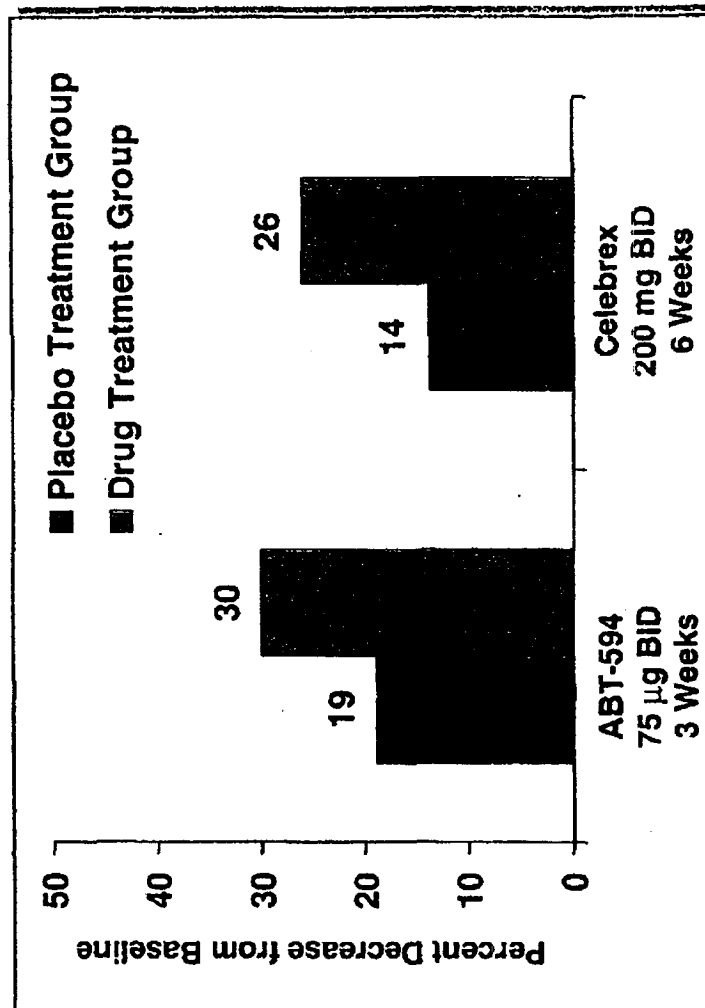
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ABBT 0021819

Cholinergic Channel Modulation

May, 2000

Efficacy of ABT-594 vs. Celebrex (Historical): WOMAC Pain Decrease from Baseline

- ABT-594 and Celebrex exhibit comparable efficacy in pain associated with osteoarthritis



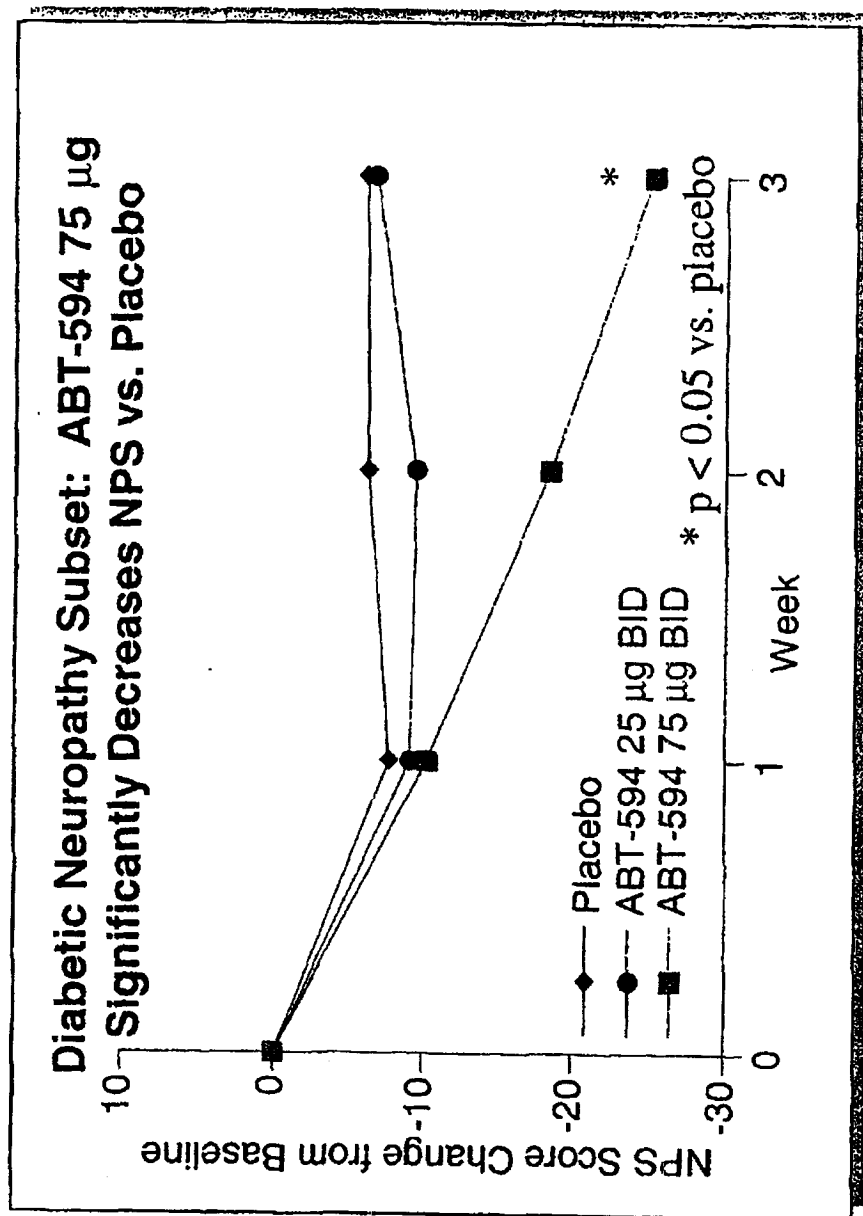
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ABBT 0021820

Cholinergic Channel Modulation

May, 2000

Diabetic Neuropathy



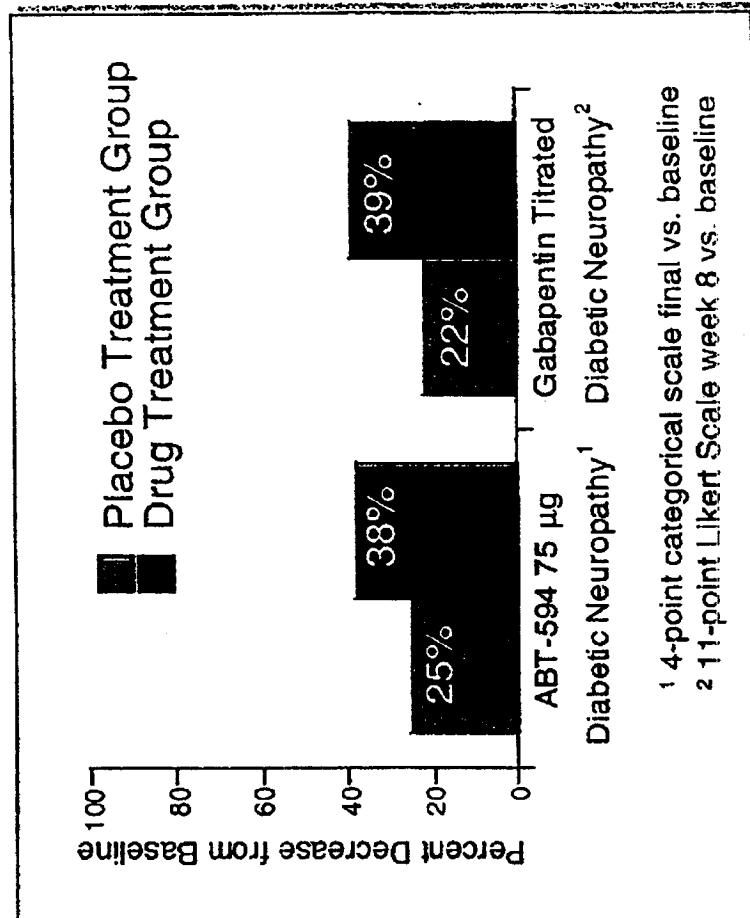
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 ABBT 0021821

Cholinergic Channel Modulation

May, 2000

Efficacy of ABT-594 vs. Gabapentin (Historical) in Diabetic Neuropathy

- Gabapentin:
 - 8 week ascending dose trial to maximum tolerated dose of gabapentin
 - 11-Point Likert scale week 8 vs. baseline
- ABT-594:
 - 3 week fixed dose trial
 - 4-Point categorical scale final vs. baseline

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ABBT 0021822

Cholinergic Channel Modulation

May, 2000

Soft Elastic Capsule is Tolerated Better Than Solution Formulation

Adverse Events

Molar Extraction

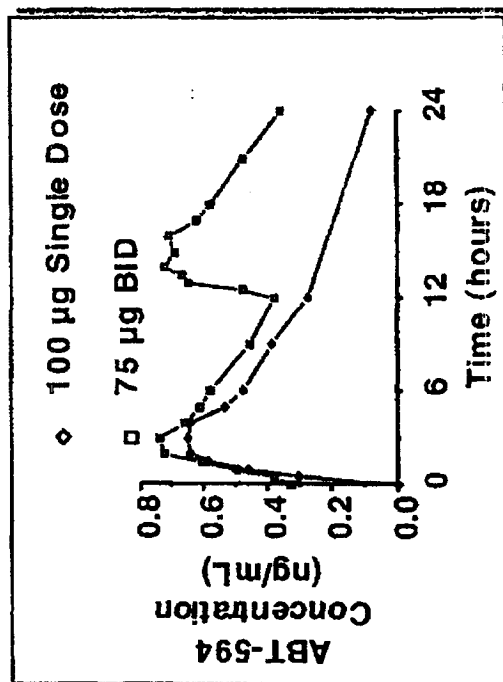
100 µg Placebo
solution

Nausea	32%	(12%)
Vomiting	20%	(2%)
Dizziness	24%	(4%)

OA and Neuropathic

75 µg BID Placebo
SEC

Nausea	15%	(3%)
Vomiting	5%	(0%)
Dizziness	7%	(5%)

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ABBT 0021823

Cholinergic Channel Modulation

May, 2000

Side Effect Profile: ABT-594 vs. Competitor Compounds

Event	Gabapentin to 3600 mg	Ultram ¹ 50-100 mg q4-6 hr	OxyContin ²	ABT-594 75 mcg BID
Confusion	8 %			0 %
Somnolence	23 %		23 %	0 %
Dizziness	24 %	31 %	13 %	7 %
Nausea	8 %	34 %	23 %	15 %
Vomiting		13 %	12 %	5 %
Constipation		38 %	23 %	1 %

¹ Chronic non-malignant pain, up to 30 days

² "Clinical trials"

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ABBT 0021824

Cholinergic Channel Modulation

May, 2000

Phase I Tolerability Trials: Hard Gelatin Capsule

- Dose titration study from 75 µg to 450 µg BID
 - Subjects ascended through 75, 150, 225, 300, 375, and 450 µg BID over 12 days, and remained at highest tolerated dose until day 18
 - 7 of 15 subjects reached 450 µg BID for duration of study
 - 13 of 15 subjects achieved 300 µg BID for duration of study
- Conclusions:
 - 300 µg BID considered maximum tolerated dose
 - Titration offered enhanced tolerability vs. 300 µg BID fixed dose study
 - Dose titration scheme would be used in Phase IIb diabetic neuropathy trial

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ABBT 0021825

Cholinergic Channel Modulation

May, 2000

ABT-594: Titration Reduces Nausea and Emesis, but not Dizziness

	M99-076 (no titration) n (%)		M99-120 (titration) n (%)	
	300 µg BID n=9	Placebo n=27	up to 300 µg BID ^a n=15	Placebo n=5
Nausea	5 (56%)	2 (7%)	5 (33%)	1 (20%)
Vomiting	4 (44%)	0 (0%)	2 (13%)	0 (0%)
Dizziness	6 (67%)	3 (11%)	10 (67%)	2 (40%)
^a For M99-120, Day 1-2: 75 µg BID; Day 3-4: 150 µg BID; Day 5-6: 225 µg BID; Day 7-8: 300 µg BID.				

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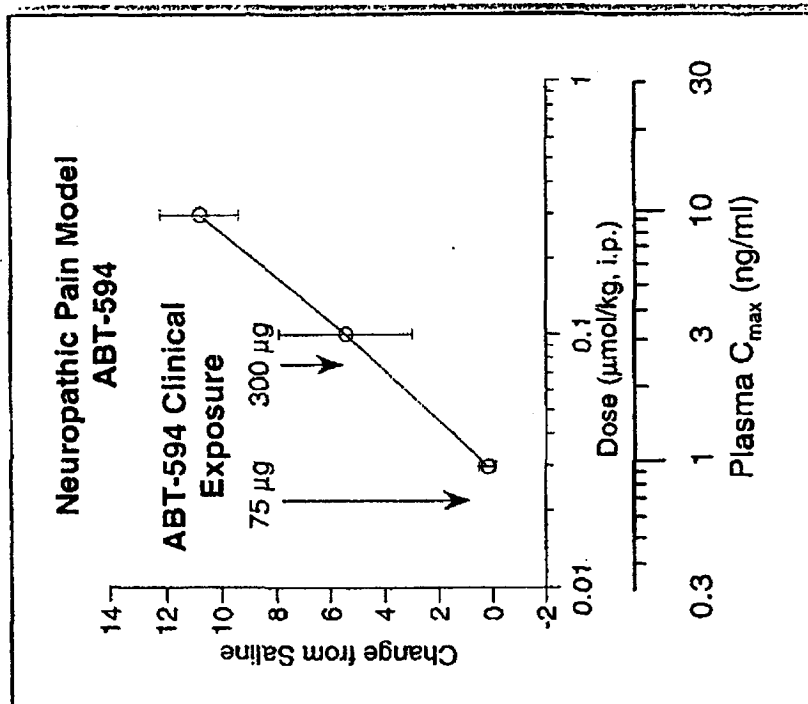
ABBT 0021826

Cholinergic Channel Modulation

May, 2000

ABT-594: Re-evaluation of MTD

- Effective clinical dose of ABT-594 (75 µg BID):
 $C_{\max} = 0.65 \text{ ng/ml}$
- Phase IIb max. dose (300 µg BID):
 $C_{\max} = 2.84 \text{ ng/ml}$
- Preclinical efficacy:
 $C_{\max} = 1 \text{ to } 5 \text{ ng/ml}$

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ABBT 0021827

Cholinergic Channel Modulation

May, 2000

Phase IIb Trial in Diabetic Neuropathy

- Initiated April, 2000
- Study design:
 - Seven weeks duration - (1 week titration, 6 week maintenance)
 - Four groups: 150 µg BID, 225 µg, BID, 300 µg BID, placebo
 - Titration scheme will be used
 - 75 µg BID x 2 days, 150 µg BID x 2 days, 225 µg x 2 days, 300 µg
- Outcome measures:
 - Primary outcome: Change from baseline of the average Daily Pain Intensity Categorical Scale
- Results expected by January, 2001

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Cholinergic Channel Modulation

May, 2000

Discovery Program Update

Goal: Identify a backup to ABT-594 exhibiting a 30-fold improvement in therapeutic index

- Impact of collaboration with NeuroSearch
 - Availability of recombinant human nAChRs
 - Availability of new proprietary structural classes
 - Opportunity for new molecular profiles and new therapeutic targets
- Progress toward identification of ABT-594 backup
 - A-312046
 - Additional leads
- New insights into the molecular target
- Program directions--beyond the ABT-594 backup
 - Analgesia
 - New indications (depression, psychosis, anxiety)

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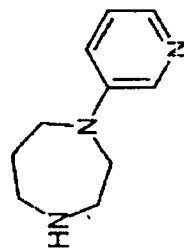
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Cholinergic Channel Modulation

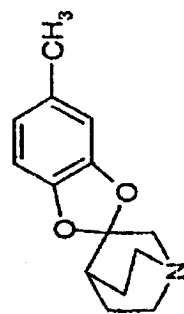
May, 2000

ABT-594 Backup: Impact of NeuroSearch Collaboration

- Re-initiation of screening against human recombinant nAChR subtypes
- Access to new proprietary structural class (homopiperazines)
 - Current lead compound: A-312046:
 - Active in models of acute, persistent and neuropathic pain
 - Retains full efficacy on repeated dosing
 - 10-fold improvement in therapeutic index vs. ABT-594
- New leads for additional neuropsychiatric indications
 - α -7 selective lead (NS-3806) active in models of depression and psychosis



A-312046



NS-3806

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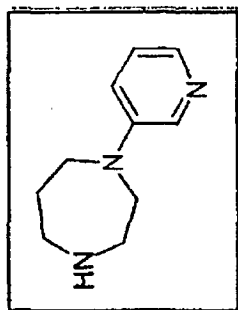
ABBT 0021830

Cholinergic Channel Modulation

May, 2000

Properties of Most Promising Compounds: A-312046

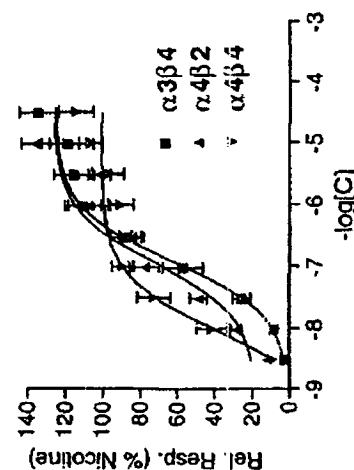
- In Vitro Profile (RLB): Comparable to ABT-594



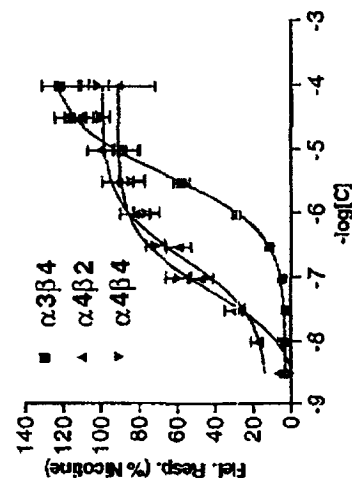
Binding Site	Ki (nM) (N)	
	ABT-594	A-312046
Cytisine Binding Site ($\alpha 4\beta 2$)	0.048 (6)	0.051 (3)
BTX Binding Site (Central $\alpha 7$)	1220 (7)	504 (3)
BTX Binding Site (Peripheral $\alpha 1$)	>10,000 (3)	7100 (3)

- In Vitro Profile (Functional): More $\alpha 4$ -selective than ABT-594

ABT-594



A-312046

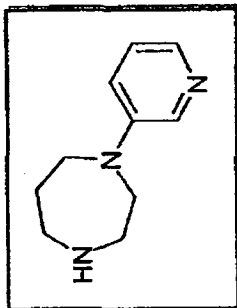
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ABBT 0021831

Cholinergic Channel Modulation

May, 2000

A-312046 In Vivo Profile: Efficacy Models



- Active in models of acute thermal pain
 - Mouse Hot Plate Assay: MED* = 6.2 μ mol/kg, i.p.
 - Rat Hot Box Model: MED* = 1.9 μ mol/kg, i.p.
- Active in models of persistent pain
 - Mouse ACA: MED* = 1.9 μ mol/kg, i.p.
 - Rat Formalin Model: MED* = 1.9 μ mol/kg, i.p.
- Active in model of neuropathic pain
 - Rat Chung Model: MED* = 0.62 μ mol/kg, i.p.

Differs from most compounds, exhibiting comparable or greater potency in neuropathic pain model vs. all other pain models

***In general, to achieve a statistically significant response, at least 50% of maximal effect is required**

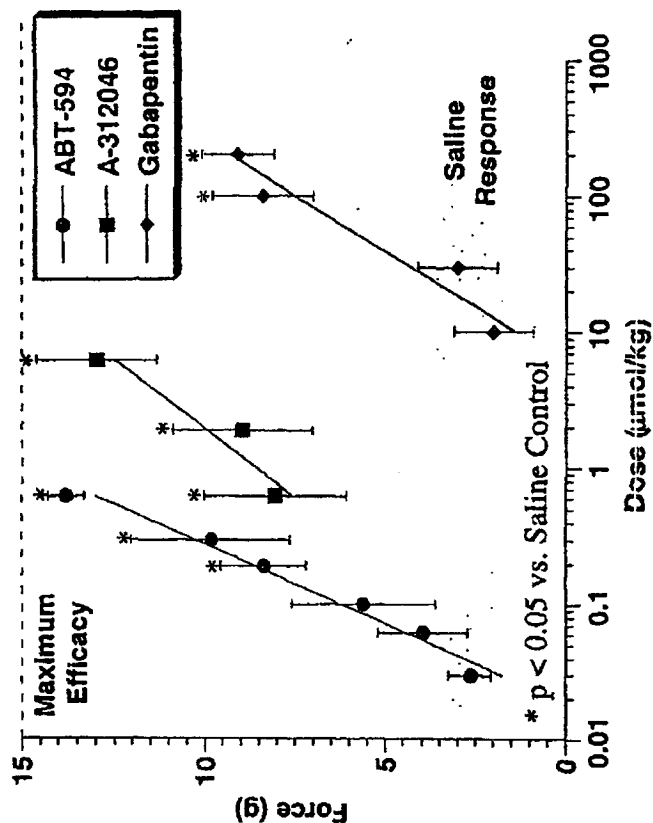
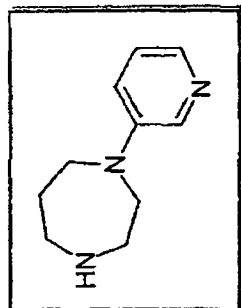
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Cholinergic Channel Modulation

May, 2000

A-312046 vs. ABT-594: Neuropathic Pain Model



- A-312046 is 3 to 10-fold less potent than ABT-594
- Qualitative assessment: Significantly fewer side effects are observed at effective doses (i.e., dyspnea, prostration)

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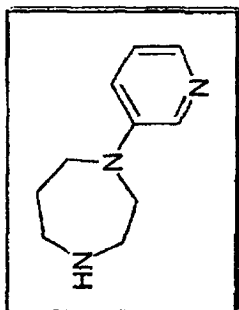
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Cholinergic Channel Modulation

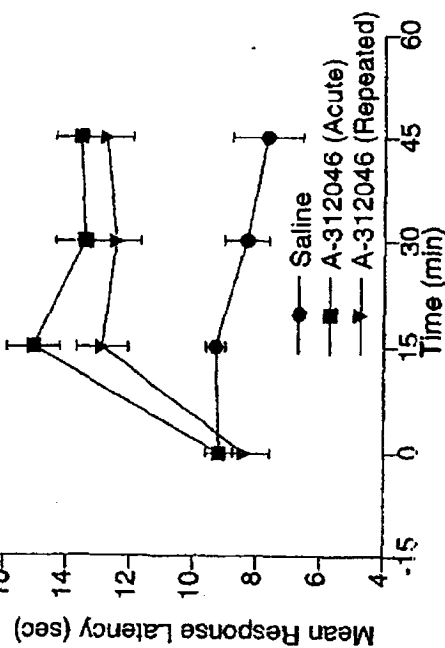
May, 2000

A-312046: Repeated Dosing Studies

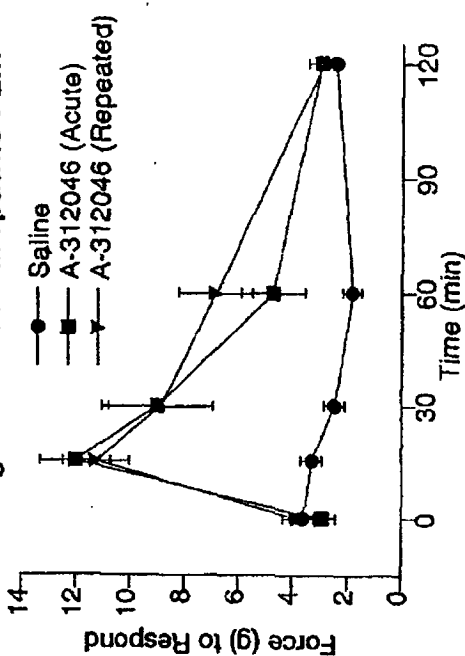
- Active upon repeated administration in rat hot box model of acute thermal pain and the Chung model of neuropathic pain



Effect of 5-Day BID Treatment with A-312046
in Hot Box Model of Acute Thermal Pain



Effect of 5-Day BID Treatment with A-312046
in the Chung Model of Neuropathic Pain

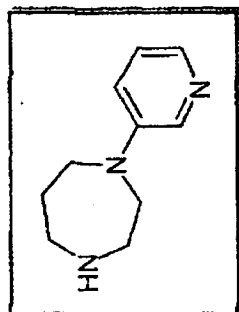


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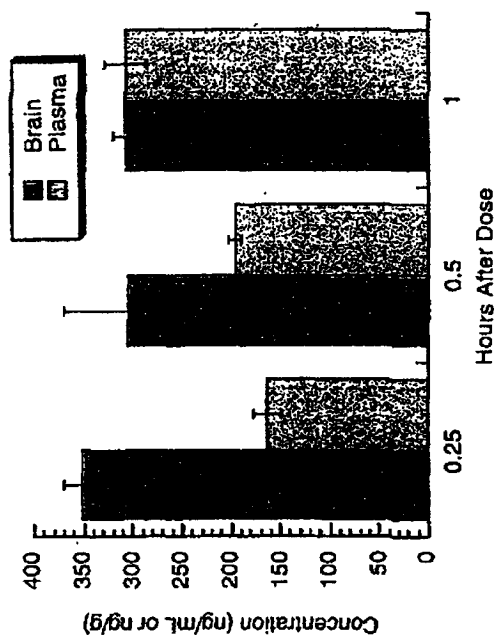
Cholinergic Channel Modulation

May, 2000

A-312046: Pharmacokinetics



- Exhibits moderate oral bioavailability (49%) in rat (ABT-594: 61%)
- Readily distributes to CNS (ABT-594: 2:1 Brain:Plasma)
- Studies ongoing to evaluate in additional species, and to repeat rat PK studies



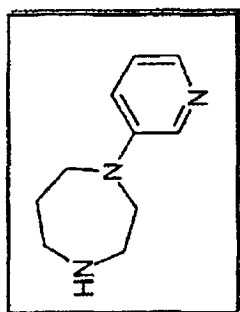
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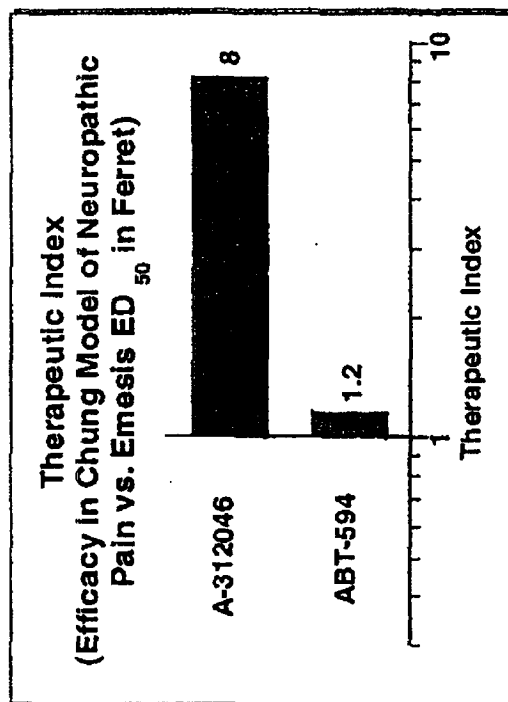
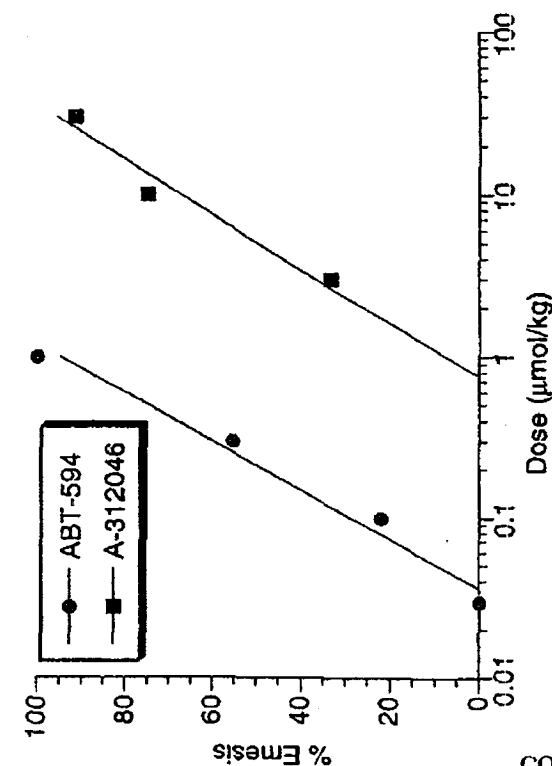
Cholinergic Channel Modulation

May, 2000

ABT-594 vs. A-312046: Emetic Liability



- In ferret model: ED_{50} for emesis shifted 24-fold (0.24 $\mu\text{mol/kg}$ vs. 5.2 $\mu\text{mol/kg}$)
- In preliminary dog study, no emesis observed at 1 $\mu\text{mol/kg}$ (ABT-594 exhibited 100% at 0.2 $\mu\text{mol/kg}$)

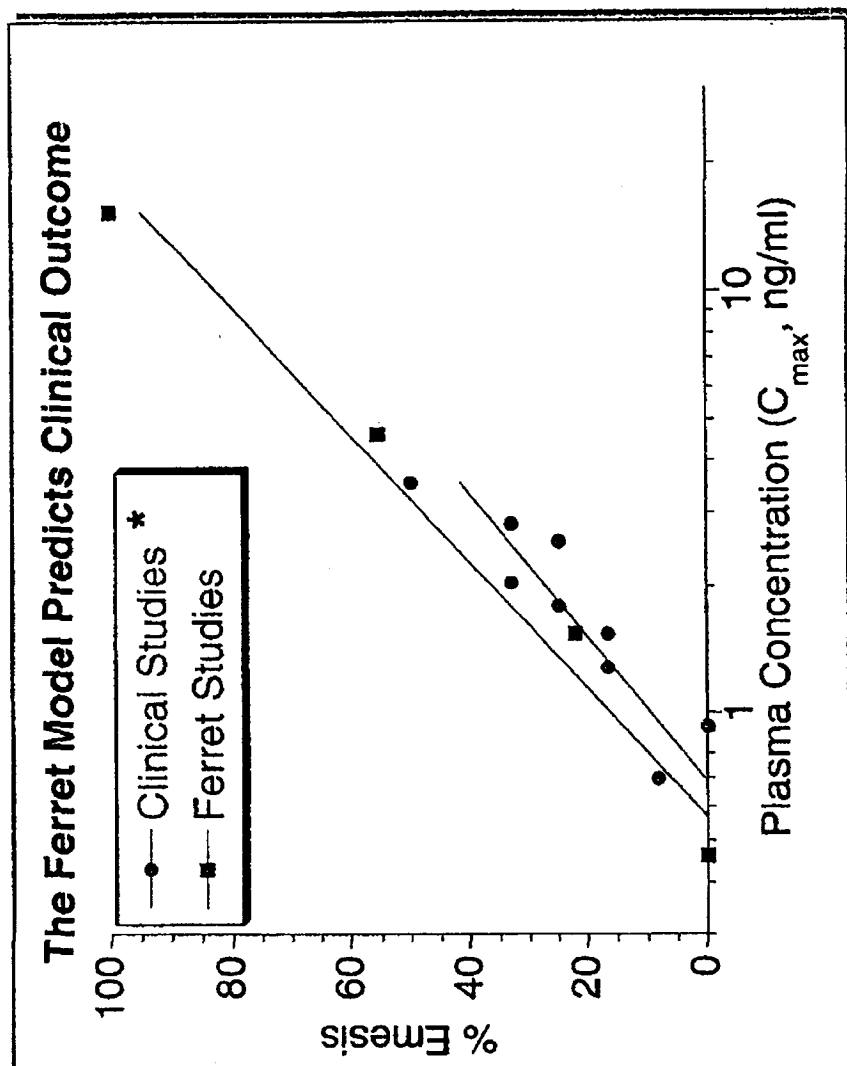
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ABBT 0021836

Cholinergic Channel Modulation

May, 2000

ABT-594 in the Ferret Emesis Model



* Day 1, untitrated (M99-076)

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ABBT 0021837

Cholinergic Channel Modulation

May, 2000

Therapeutic Index Comparison: ABT-594 vs. A-312046

- Therapeutic index based on ratio of dose for adverse event and MED (~50% Max. resp.) in Chung neuropathic pain model

	Adverse Event	Therapeutic Index		Relative Improvement
		ABT-594	A-312046	
Ferret	Emesis	1.2	8	7x
Mouse	Seizure	10	500	50x
	Threshold			
	ALD	100	480	5x
	Rotarod Performance	10	100	10x
Rat	Balance (Edge Test)	0.5	30	60x

22

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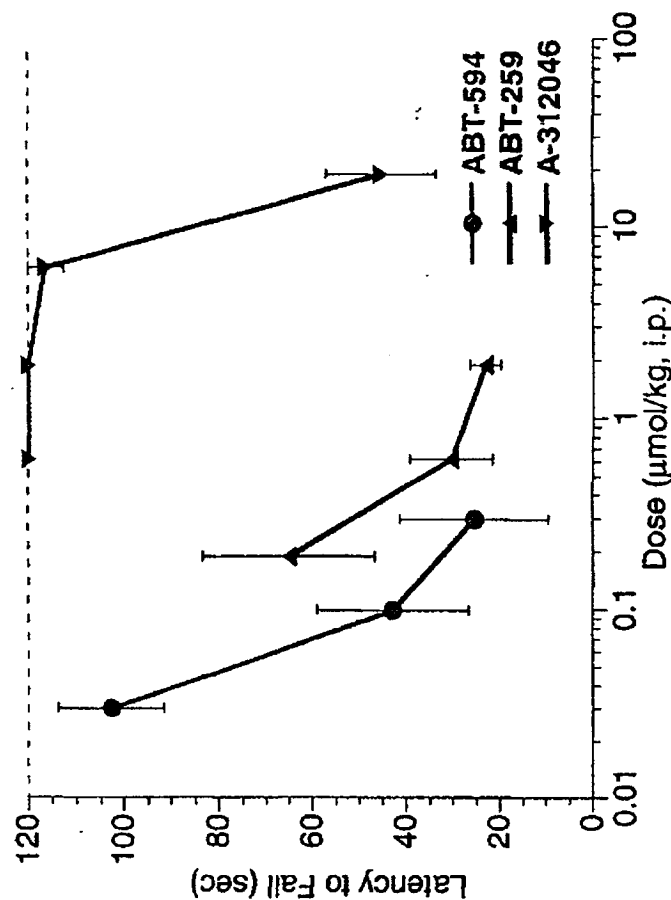
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Cholinergic Channel Modulation

May, 2000

A-312046 in Rat Edge Test of Coordination and Muscle Strength

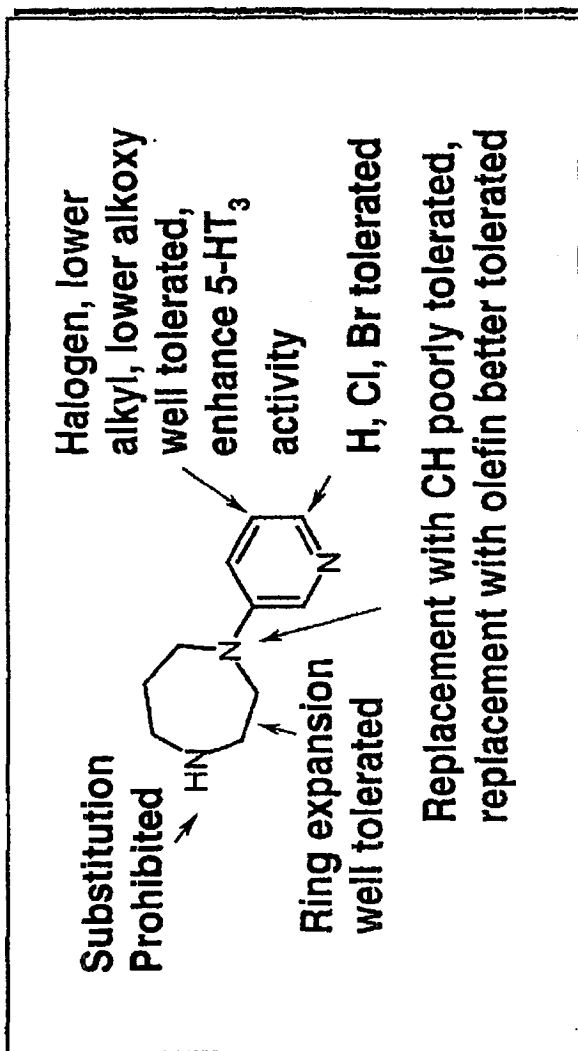
- Model developed within project as an alternative to literature muscle strength assays (screen test)
- Has not been validated with compounds known to clinically affect coordination, muscle strength, dizziness, etc.

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ABBT 0021839

Homopiperazine Series SAR

- Evaluated ~75 analogs
- SAR trends similar to ABT-594 series
- Compounds generally highly selective for nAChRs, but 5-HT₃ antagonist activity can be introduced

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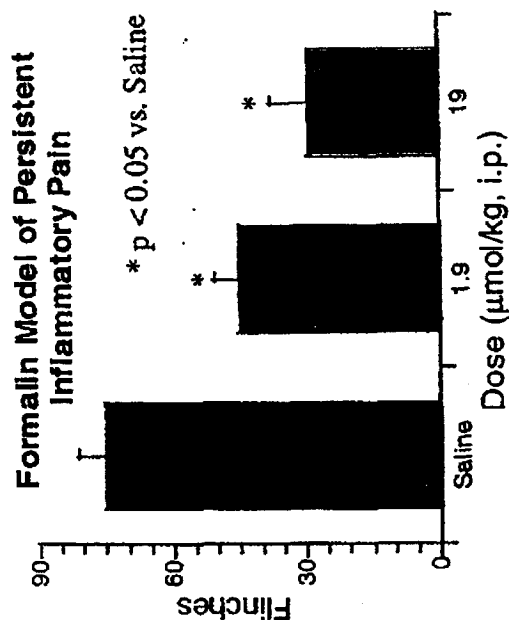
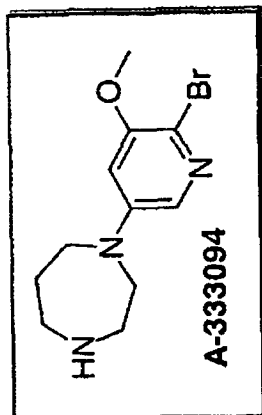
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Cholinergic Channel Modulation

May, 2000

Homopiperazine Series: Additional Leads

- A-333094:
 - Better efficacy and potency in inflammatory vs. neuropathic pain models
 - Comparable potency to A-312046 in Formalin model
 - Improved emetic profile vs. A-312046 ($ED_{50} = 30 \mu\text{mol/kg}$ vs. $5.2 \mu\text{mol/kg}$ for A-312046)
 - Moderate 5-HT_3 antagonism activity
 - ALD, seizure threshold $\sim 450 \mu\text{mol/kg}$

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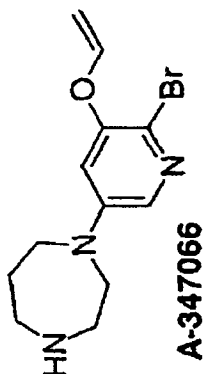
Cholinergic Channel Modulation

May, 2000

Homopiperazine Series: Additional Leads

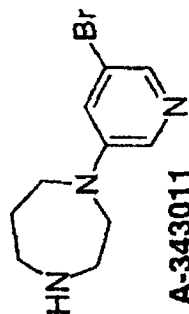
- A-347066:

- Potent ancillary activity as 5-HT₃ antagonist (may contribute to decreased emetic liability)
- Preliminary data show activity across pain models



- A-343011:

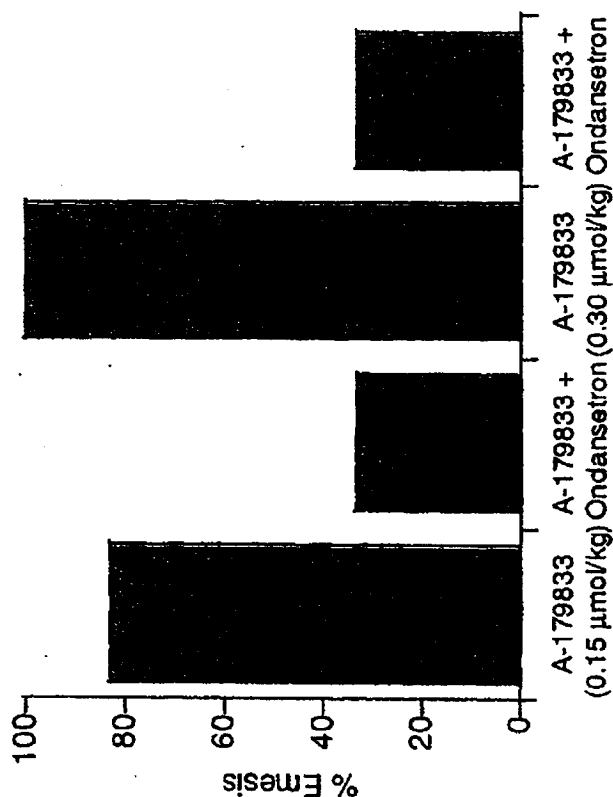
- Similar to A-312046 but with decreased efficacy at $\alpha 3\beta 4$ nAChR subtype

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ABBT 0021842

Does 5-HT₃ Antagonism Block nAChR-mediated Emesis?

- A-179833:
 - Selective, highly emetic nAChR agonist
 - Emesis fully blocked by nAChR antagonists
- Potent and selective 5-HT₃ antagonist ondansetron partially blocks A-179833 induced emesis



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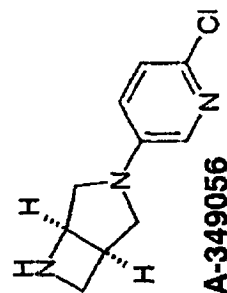
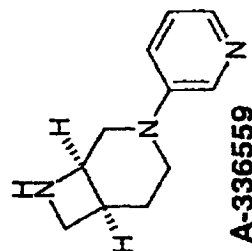
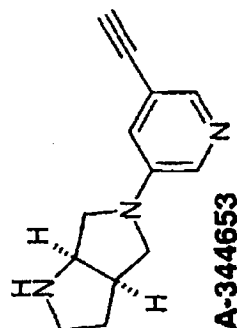
ABBT 0021843

Cholinergic Channel Modulation

May, 2000

ABT-594 Backup: Additional SAR Development

- 3.3.0-Diazabicyclooctane Series:
 - Evaluated 15 analogs - A-344653 best to date
 - Structurally distinct
 - Active in persistent and neuropathic pain models
- 4.2.0-Diazabicyclooctane Lead:
 - High affinity and potency
 - In vivo efficacy in pain models
 - Low incidence of behavioral side effects
- 3.2.0-Diazabicyclooctane Lead:
 - Excellent potency and efficacy in pain models

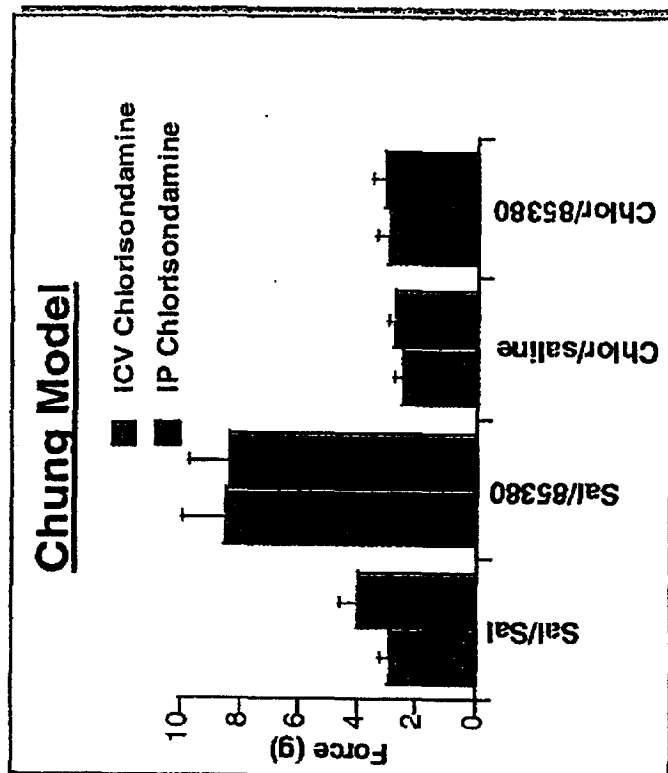
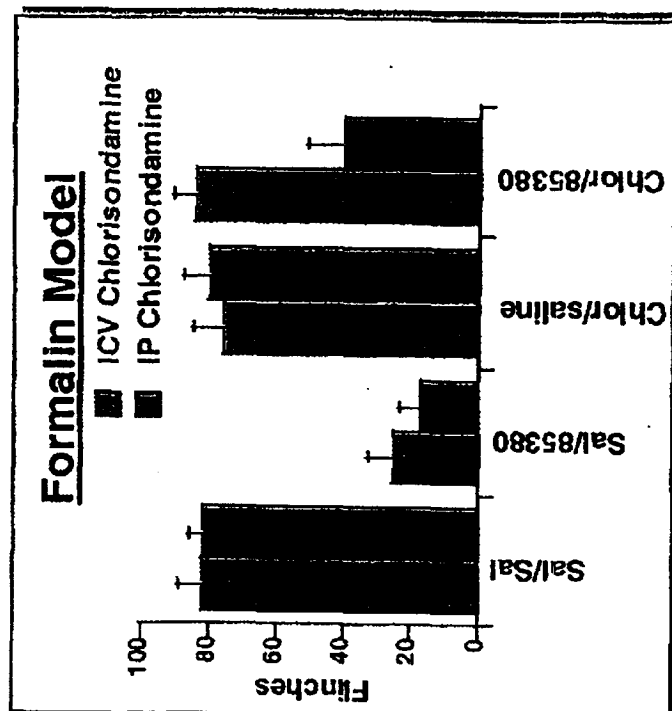
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ABBT 0021844

May, 2000

Molecular Target: New Insights

- The $\alpha 4\beta 2$ subtype is clearly implicated in acute antinociception
- In models of persistent pain (Formalin model) and neuropathic pain (Chung model), other subtypes and/or sites of action may also be implicated
- Chlorisondamine antagonism studies:

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ABBT 0021845

Subtype Selective nAChR Modulators: New Indications

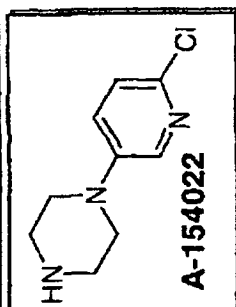
- nAChRs are modulators of neurotransmitter release
 - DA, NE, 5-HT, ACh, GABA, Glutamate, SP, CGRP...
- Different nAChR subtypes differentially regulate NT release
- Epidemiological evidence for increased nicotine use in:
 - Schizophrenia
 - Depression
 - Anxiety
- Efficacy of nicotine patch in adult ADHD
- Nicotine withdrawal precipitates depressive episodes
- Evidence for mutations of $\alpha 7$ gene in subset of schizophrenics

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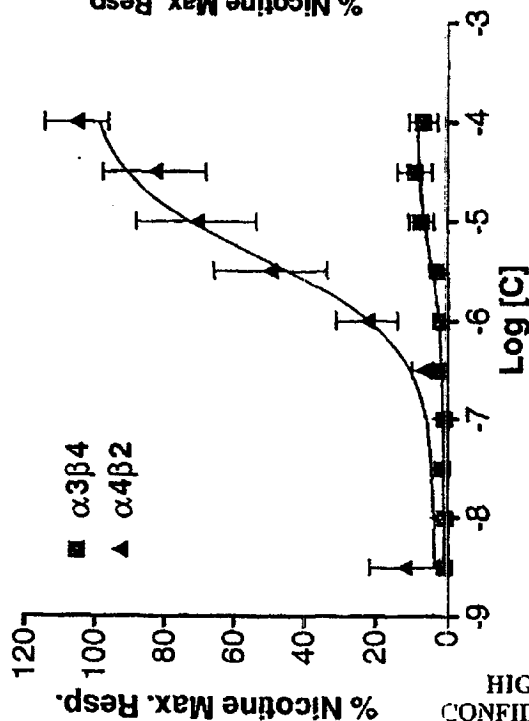
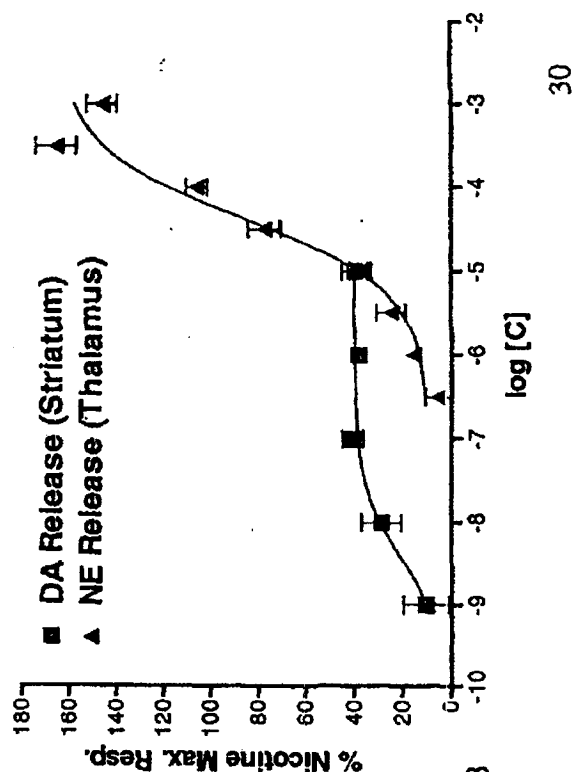
ABBT 0021846

Cholinergic Channel Modulation

May, 2000

A-154022: ChCM Library Screening Lead

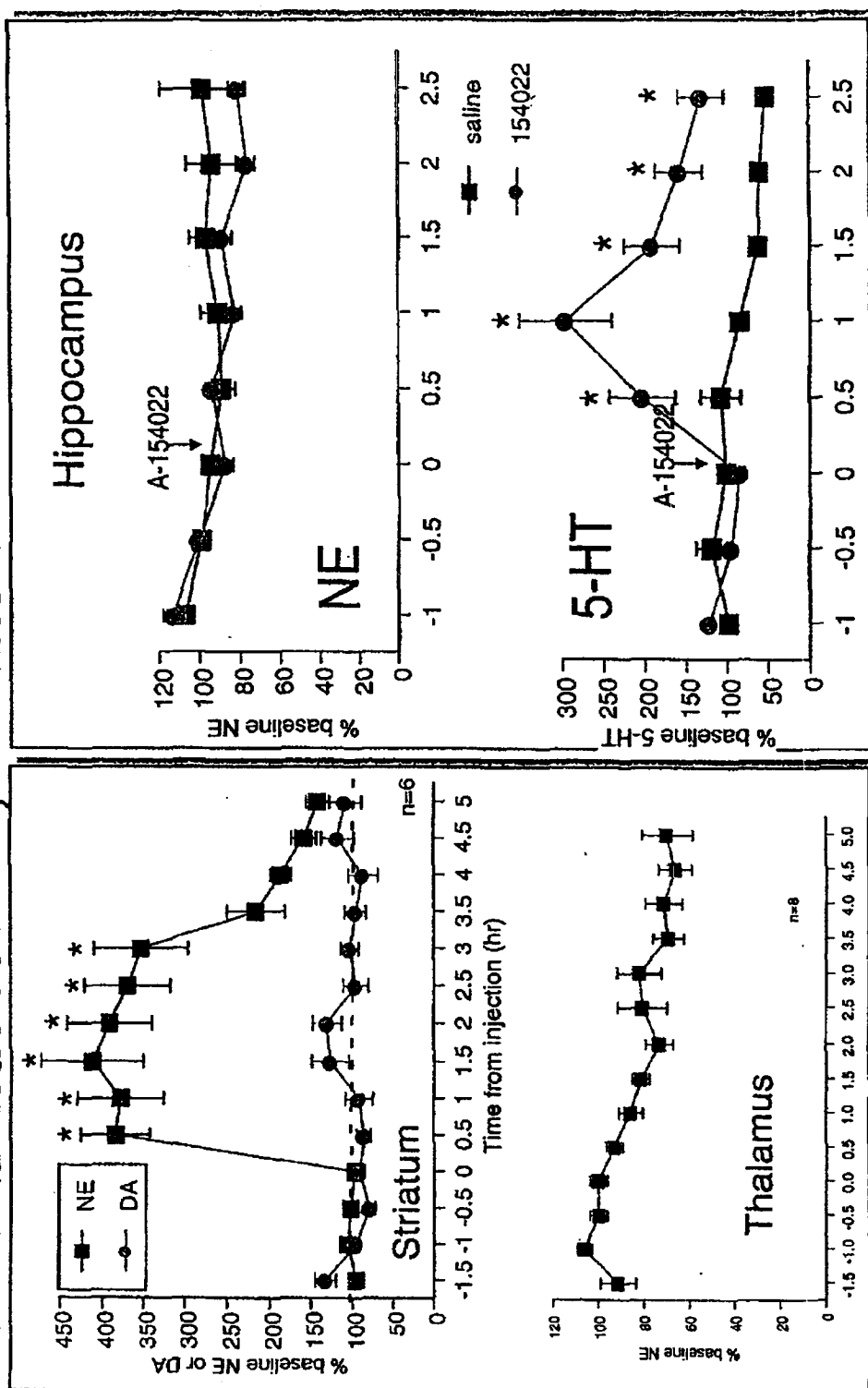
- Initially identified as $\alpha 4$ -selective ligand
- Weak, but selective 5-HT uptake inhibitory activity
- Highly selective for nicotinic vs. panel of GPCR, ion channel sites
- Exhibited efficacy in pain models, but only at relatively high dose

Calcium FluxNeurotransmitter ReleaseHIGHLY
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ABBT 0021847

Cholinergic Channel Modulation

May, 2000

A-154022-induced NE, DA and 5-HT Release in vivo

31

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ABBT 0021848

Cholinergic Channel Modulation

May, 2000

Program Summary

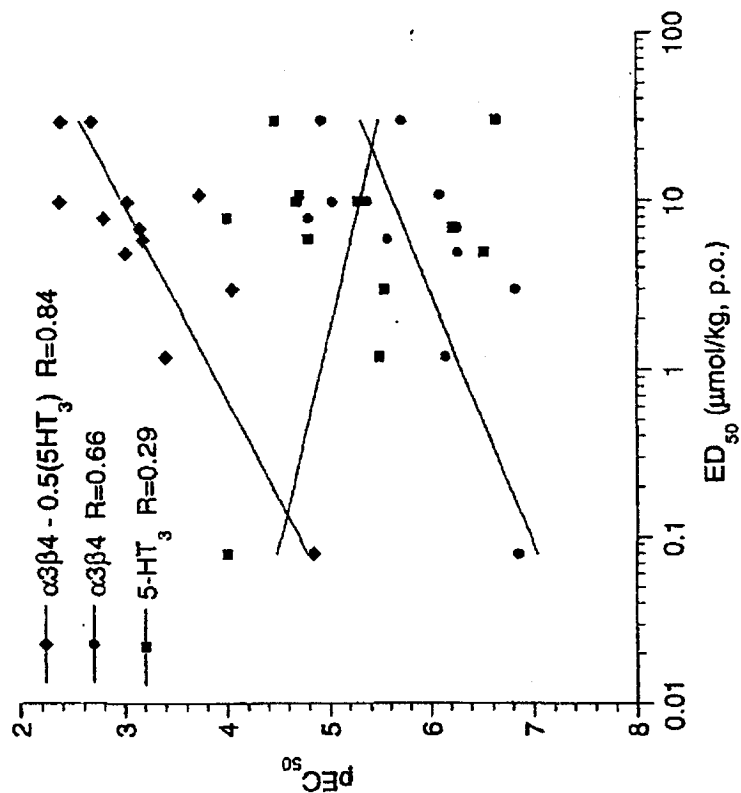
- Clinical efficacy achieved with 75 µg BID dose of ABT-594 in diabetic neuropathy
 - Additional Phase I trials indicate up to 300 µg BID well tolerated
 - Phase IIb trial in diabetic neuropathy ongoing
- Progress toward ABT-594 backup:
 - Collaboration with NeuroSearch established providing access to human recombinant nAChRs, new proprietary structural classes
 - A-312046 identified, characterization continuing
 - Additional series optimization ongoing, other structural classes
 - DDC by 4Q/00 anticipated
- New therapeutic indications
 - Depression, schizophrenia, anxiety targeted
 - Leads identified, validation ongoing

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ABBT 0021849

Does addition of 5-HT₃ antagonist activity affect emetic liability?

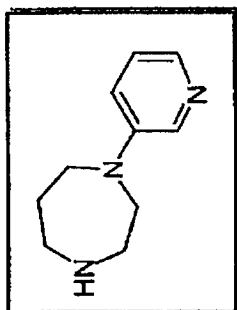
- Activity at the $\alpha 3\beta 4$ subtype positively correlates to emetic liability
- Antagonist activity at 5-HT₃ negatively correlates to emetic liability
- Factoring in both activities improves the correlation



Cholinergic Channel Modulation

May, 2000

A-312046: Safety Profile in Mice



	ABT-594 ($\mu\text{mol/kg}$, i.p.)	A-312046 ($\mu\text{mol/kg}$, i.p.)	Relative Potency
Seizure Threshold	1.9	320	170
ALD	19	300	16
Rotarod Performance	1.9	62	33
Edge Test (Rat)	0.10	19	100

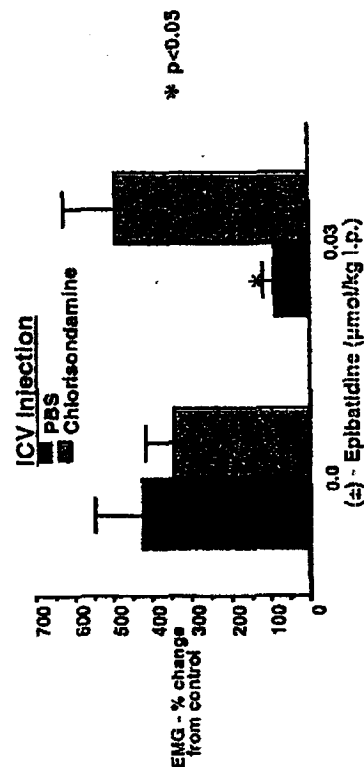
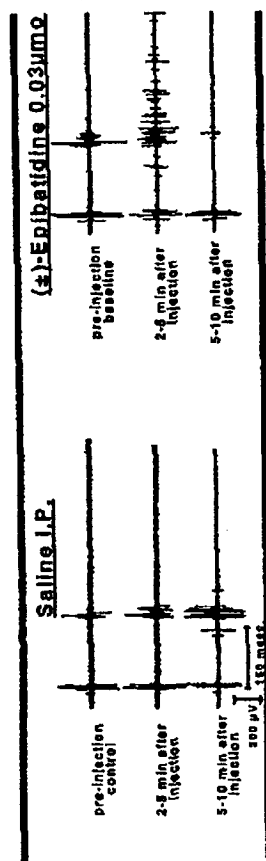
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ABBT 0021851

Cholinergic Channel Modulation

May, 2000

C-Fiber spinal flexor reflex model

- Epibatidine produces suppression of C-fiber EMG response
- Effect is fully blocked by central nAChR blockade

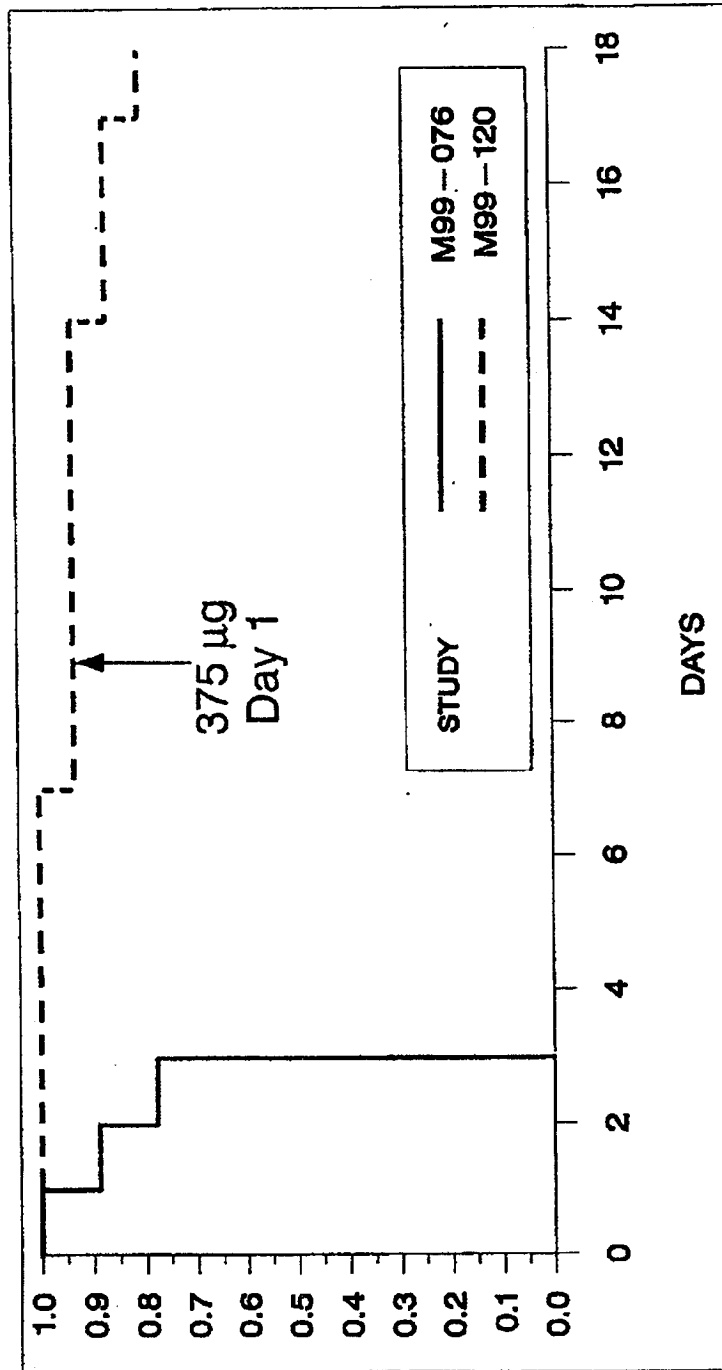
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ABBT 0021852

Cholinergic Channel Modulation

May, 2000

Time to Discontinuation: M99-076 vs. M99-120, 375 µg



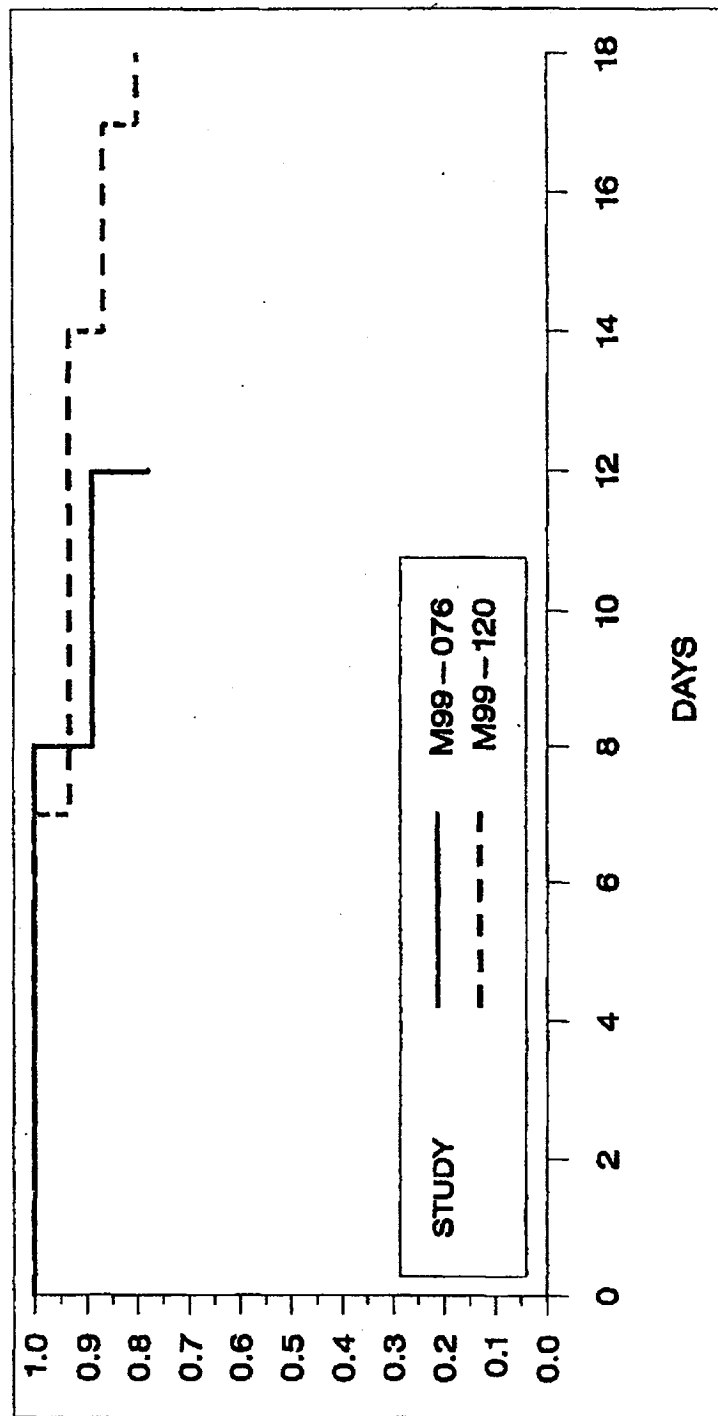
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ABBT 0021853

Cholinergic Channel Modulation

May, 2000

Time to Discontinuation: M99-076 vs. M99-120, 300 µg



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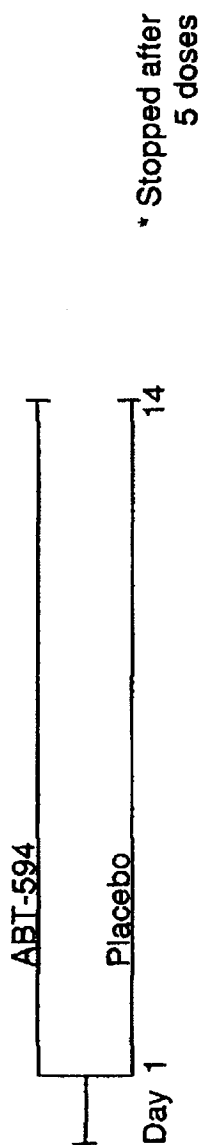
ABBT 0021854

Cholinergic Channel Modulation

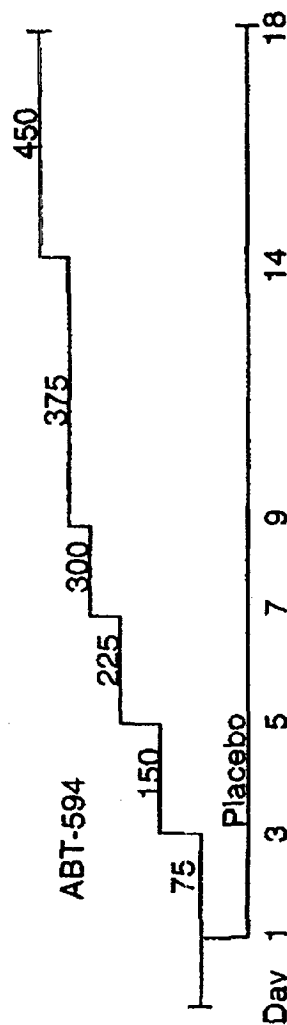
May, 2000

Study Design

- M99-076 (fixed dose)
 - n=12/group: 9 ABT-594 (titrated dose), 3 Placebo
 - 9 Groups (mcg BID): 75, 100, 125, 150, 175, 200, 250, 300, 375*



- M99-120
 - n=20: 15 ABT-594 (mcg BID), 5 Placebo

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ABBT 0021855

Cholinergic Channel Modulation

May, 2000

Demographics

M99-076		M99-120	
Fixed Dose		Titrated Dose	
ABT-594	Placebo	ABT-594	Placebo
n=81	n=27	n=15	n=5

Gender

Male	63 (77%)	22 (81%)	13 (87%)	5 (100%)
Female	18 (22%)	5 (18%)	2 (13%)	0 (0%)

Age

(mean, years)

34	35	36	31
----	----	----	----

Weight

(mean, kg.)

79	77	76	84
----	----	----	----

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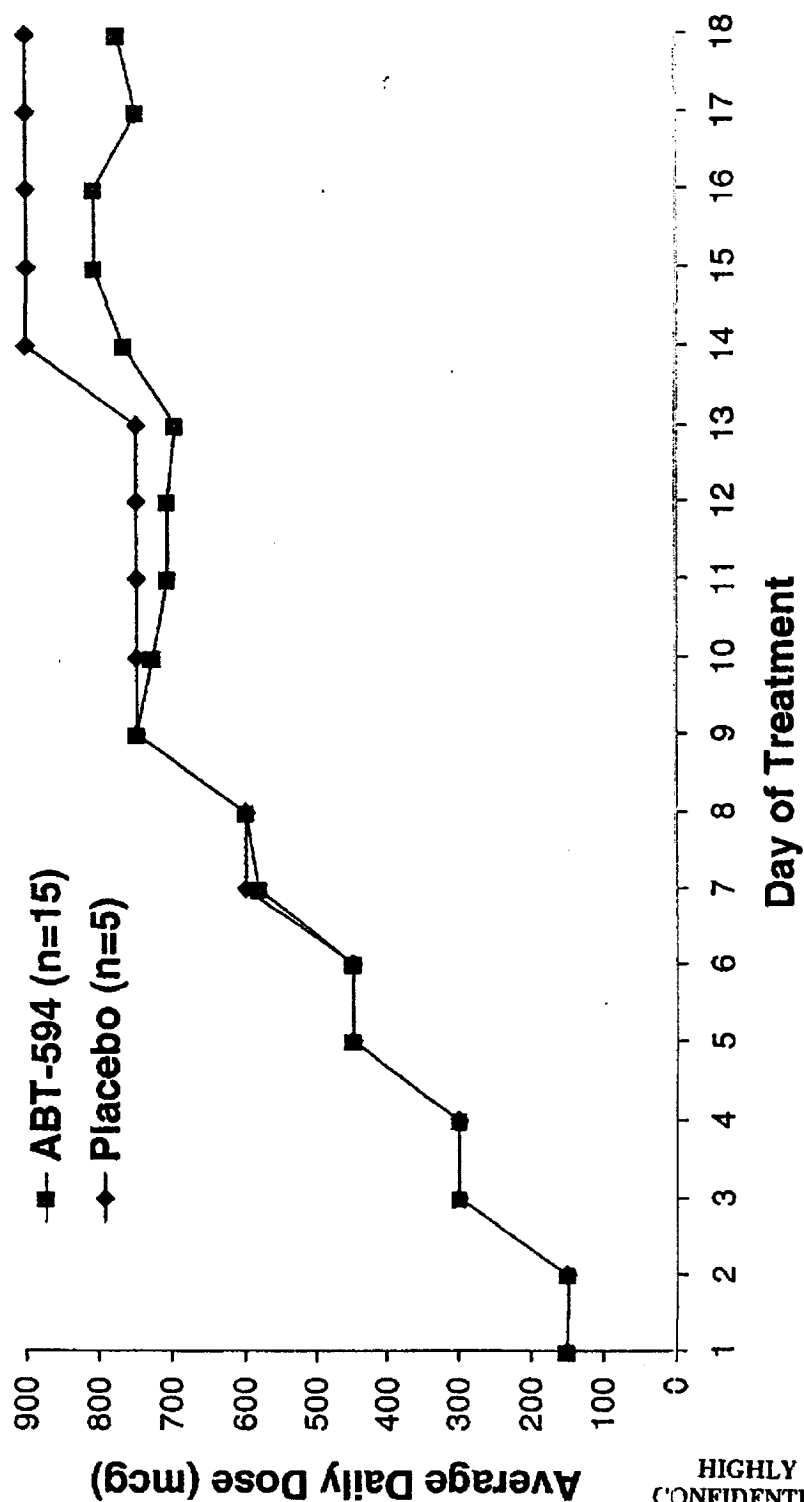
ABBT 0021856

Cholinergic Channel Modulation

May, 2000

M99-120

Average Daily Dose



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ABBT 0021857

Cholinergic Channel Modulation

May, 2000

ABT-594 Titration Effect***150 mcg BID AE Prevalence, Day 1-4***

	M99-076		M99-120	
	(no titration)		(titration)	
	n (%)		n (%)	
	150 mcg BID	Placebo	up to 150	mcg BID^a
Placebo	n=9	n=27	n=15	n=5
Nausea	2 (22)	2 (7)	2 (13)	0 (0)
Vomiting	1 (11)	0 (0)	1 (7)	0 (0)
Dizziness	3 (33)	1 (4)	3 (20)	1 (20)

^a For M99-120, Day 1-2: 75 mcg BID; Day 3-4: 150 mcg BIDHIGHLY
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ABBT 0021858

Cholinergic Channel Modulation

May, 2000

ABT-594 Plasma Concentrations***Study M99-076, Day 14***

Dose	C_{\max} (ng/mL)
75 mcg BID	0.7
150 mcg BID	1.54
300 mcg BID	2.84

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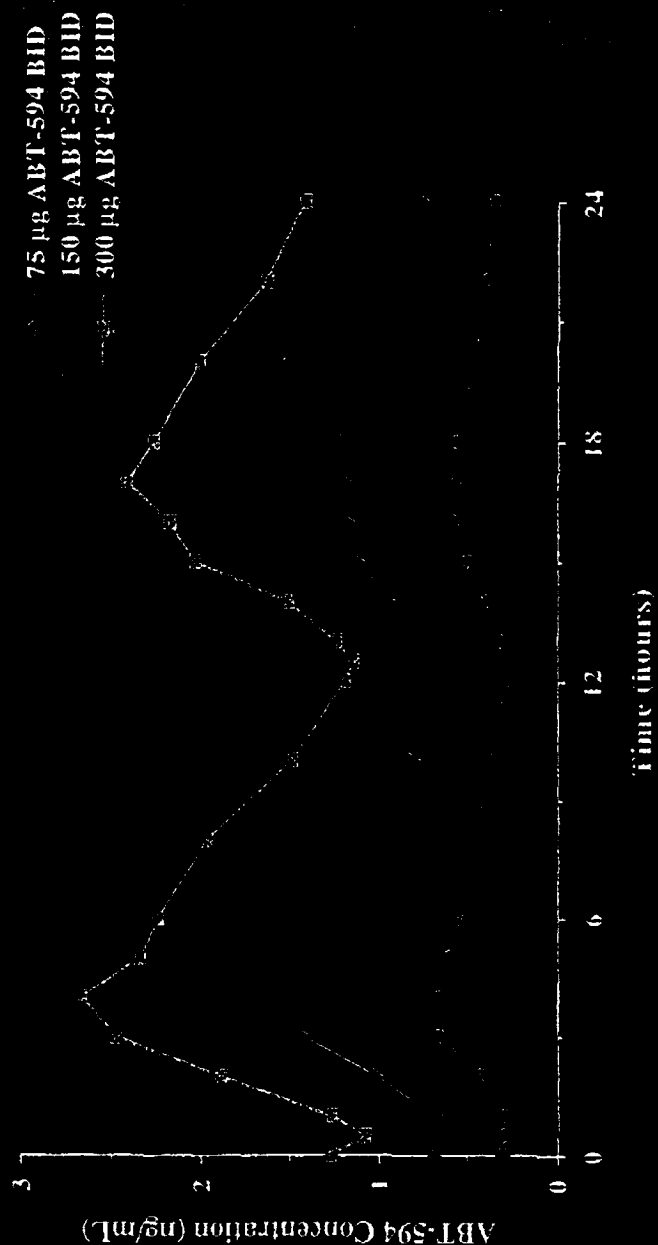
ABBT 0021859

Cholinergic Channel Modulation

May, 2000

ABT-594 Plasma Concentrations

Study M99-076, Day 14



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ABBT 0021860

McCarthy Deposition Exhibit 14

P's Exhibit CE

June 2000
ABT-594 Project Status Report

Monthly Highlights

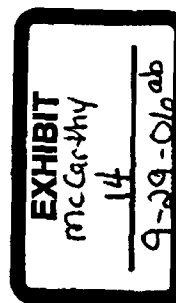
- Experimental placebo manufacturing run prepared at PPD's Puerto Rico Manufacturing Plant (AHP1) in the Potent Drug Module. Special thanks to Serafin Torres and the API plant personnel, and PARC team members Rhonda Peck, Erskine Hilyer and Ji Zhou for their commitment and long hours!
- Enrollment in M99-114 is slower than planned and is under scrutiny by team personnel. (See July Progress Gauges below.)

Key Progress Gauges - June Accomplishments	Target Date	Status
Begin testing for release and stability initiation of the 3 NDA lots of drug substance	6/5	Incomplete - Delay due to specification system issues (see below) Revised Target: 7/21
Issue new drug substance test document	6/5	Incomplete - Delay due to issues surrounding new specification documentation system. Revised Target: 7/21
Complete Development Plan preparation meetings	6/16	Complete
90 patients enrolled M99-114	6/25	Incomplete - 73 enrolled as of 6/30
2/3 of sites actively enrolling patients M99-114	6/25	Incomplete - 18 / 29 sites actively enrolling, 24 / 29 sites actively screening
Obtain validated results for ICH Category 1 solvent DCE in 594 clinical drug substance lots and starting material	6/25	In Process
Discovery Project Team to identify 3 potential follow-on compounds for advanced preclinical characterization	6/30	Complete
Develop cholinergic channel modulator scientific franchise strategy	6/30	Complete
Complete preparation for experimental capsule manufacturing run at AHP1 (800) to assess environmental/employee exposure	6/30	Complete

July Projections	Target Date	Status
Contact all M99-114 investigators to determine enrollment obstacles	7/5	
Review early terminations and Adverse Event profile to determine strategic options to address slow enrollment	7/12	
Finalize recommendations and initiate recommended strategies	7/21	
Issue new drug substance test document	7/21	
Begin testing for release and stability initiation of the 3 NDA lots of drug substance	7/21	
90 patients enrolled M99-114	7/31	
Schedule active capsule experimental manufacturing run at AHP1 for 8/00	7/31	

1 of 7

ABT 0004422
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McCarthy Deposition Exhibit 18

P's Exhibit CR



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
08/31/2000 12:03 PM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
cc Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject M99-114 Extension letter

Chris -

Here's a copy of the extension letter for your review. Bruce has seen it and his comments have been incorporated.....mc



extension letter.doc

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ABBT241301



August 31, 2000

<Investigator Name>
<Address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr.:

I am pleased to inform you that the enrollment period for study M99-114 has been extended. The last day for randomization will be March 2, 2001. If we reach our target enrollment before that date the study will be ended at the time when 320 subjects are randomized.

While it may now seem that we have a bit of breathing room, in actuality we don't. The holidays are fast approaching - a time when recruitment and enrollment slows down considerably. We will, in effect, be losing approximately 2 months of our enrollment extension to the holiday season. That will leave us with just 3 ½ months of remaining optimal recruitment time. To put this in perspective, in the last 3 ½ months of this study approximately 110 subjects were randomized. If we enroll the same number during the optimal recruitment period of the enrollment extension, we will have a total enrollment of 240 - 80 subjects short of our goal. These numbers indicate a need to remain focused on recruitment efforts before and after the holiday season.

We expect the holiday season to be challenging in terms of recruitment and enrollment, however, there may be an advantage for many subjects to enroll during this time. If a subject receives pain relief from the study medication, their holidays would be more enjoyable. In addition, subjects should be able to determine whether or not they will tolerate the drug within the first week of therapy. With careful planning of randomization dates, the issue of tolerability is unlikely to interfere with the subjects' holidays.

Please continue to use the upcoming weeks to concentrate your efforts on maximum recruitment and enrollment. Please continue to call us with your enrollment questions. The Analgesia Venture at Abbott Laboratories thanks you for your continuing efforts to make study M99-114 a success.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT241302

McCarthy Deposition Exhibit 19

P's Exhibit CV

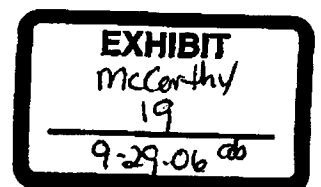
**Clinical Trial Recruitment
and Centralized Screening Program
For Painful Diabetic Neuropathy**

**Developed for Abbott Laboratories
September 28, 2000**

© Phone Screen and GCI Healthcare Clinical Trial Recruitment
Page 1 of 9

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ABBT233741



Executive Summary

Abbott Laboratories is conducting a multi-center, randomized, double blind, placebo-controlled study investigating the efficacy and safety of ABT-594/M99-114 in subjects with painful diabetic neuropathy (PDN). To date, 29 U.S.-based clinical research sites have accrued approximately 151 of the needed 320 patients. The deadline for enrolling the balance of 169 subjects has been extended until March 2, 2000. Study centers will continue to use site-directed methods for recruitment, so it is anticipated that additional patients will be accrued by sites over the next five months.

In an effort to complete enrollment by the March deadline, Abbott Laboratories has asked Phone Screen (a medical call center specializing in clinical trial recruitment) and its partner GCI Healthcare Clinical Trial Recruitment (a subsidiary of Grey Worldwide which implements marketing-oriented recruitment acceleration initiatives) to develop recommendations to maximize timely delivery of the needed study subjects. As Abbott anticipates that the sites will deliver about 69 patients on their own, the recommendations are designed with a recruitment goal of approximately 100 additional subjects. Abbott has stated that the current 34% dropout rate is considered in this goal number.

Key Enrollment Challenges

While painful diabetic neuropathy is a debilitating condition that has a significant impact on quality of life, study sites are confronted with a number of issues that have affected subject accrual. These issues include:

- High study dropout rate of 34% primarily due to side effects of the investigational drug
- High level of screen failures (50%)
- An older population cohort (as defined by the incidence of PDN) resulting in medical exclusion due to co-morbidities
- Other restrictive inclusion/exclusion criteria
- A general unwillingness by otherwise qualified candidates to washout of pain medication the week prior to start-up
- Patients are hesitant to participate in a placebo-controlled study
- Ongoing competitive studies at the study site or within the study market, all vying for the same patient pool
- Diabetic neuropathy is often undiagnosed by PCPs who are the primary manager of people with diabetes

Key Learnings from Study Sites

During preparation of this proposal, GCI Healthcare contacted three study centers (Dr. Backonja's site, Dr. Gibson's site and Dr. McGill's site) to benefit from their insights on recruitment for this study. The following represent key learnings from these conversations:

- Study sites feel that radio ads will be successful in reaching potential study subjects
- The typical study subject is a retiree
- Primary motivators for entering the study are:
 - Desire for pain relief
 - Free study medication
 - Compensation for study visits
- Patients often express satisfaction with their current pain medication without realizing that they are most likely not getting much pain relief, and the Abbott study may provide the opportunity for improvement.

These insights will help drive the creative direction for development of the radio ad.

Program Strategy

- To use proven communications vehicles to generate a high volume of pre-qualified referrals in the shortest time possible
- To minimize time spent by site personnel in early screening phases of recruitment, allowing them to focus their efforts on only the most qualified candidates
- To establish excellent relationships with the study sites in order to foster an atmosphere of commitment and responsibility to the study
- To develop and implement a referral management and tracking system to ensure that all leads are processed in a timely manner

Summary of Tactical Execution

Phone Screen and GCI Healthcare have developed an accelerated recruitment program, which relies on the following Core Program components:

- Radio advertising
- Centralized call center that will manage and track all referrals from the radio ads
- Targeted direct mail component
- Study site and IRB relations
- We have also recommended a Direct Mail Campaign and "pilot" Physician Referral Expansion Program as a supplementary effort for consideration by Abbott.
- Market Mapping

These recommendations are designed to provide aggressive recruitment support to 29 of the 30 study sites, as requested by the Abbott Team. However, based on the available budget, Abbott may wish to support a select subgroup of these 29 sites. In an effort to assist with the selection process, GCI Healthcare has tentatively ranked the sites (Tier 1, Tier 2 or Tier 3) based on:

- Readily available data relative to diabetes prevalence
- The number of study sites in each market – giving higher priority to metro areas with multiple sites
- Areas with higher number of retirees

Refinements to this ranking may be necessary, as Abbott may have insights about specific study sites. GCI has built additional market mapping research into the budget.

Budget

The attached spreadsheet, which itemizes the budget, assumes that advertising support will be provided to all 29 sites. Once Abbott is able to determine how many sites to support, a final budget will be submitted.

Conclusion

Phone Screen and GCI Healthcare are poised to move forward upon approval of these recommendations and look forward to working with the Abbott Team as the study moves forward.

Recruitment Estimate Funnel

GCI Healthcare estimates that the recruitment program will need to generate 2,500 calls to the 800 number in order to meet the enrollment goal of 107 patients. The estimation of call response is determined using a funnel with dropout rates anticipated at several junctures along the way. The following are our assumptions and rationale for our call response estimates:

- **Adults age 50+ in study markets with diabetes: (1,867,865):** This is the total number of adults age 50+ with diabetes who reside in markets in which the study is being conducted.
- **Adults age 50+ in study markets with diabetic neuropathy 45%: (840,539):** Of the total number of adults age 50+ with diabetes who reside in the study markets, we estimate that 45% have diabetic neuropathy.
- **Adults age 50+ in study markets with painful diabetic neuropathy 10%: (84,053):** Of the total number of adults age 50+ with diabetes/diabetic neuropathy who reside in the study markets, Abbott has estimated that 10% have *painful* diabetic neuropathy.
- **Advertising will reach 50% at least three times: (42,026):** This is the proportion of patients 50+ with painful diabetic neuropathy residing in the study markets who will be exposed to the radio ad 3 or more times. Three exposures are considered a minimum level for generating a response. The calculation excludes those who are exposed only once or twice. The rationale is that the first or second exposure to the ad raises awareness of and interest in the message in preparation for taking action – in this case, calling the toll-free study number.
- **Estimated call response rate 6%: (2,552):** A number of motivational and situational, as well as health, factors influence an individual's response to a clinical trial recruitment advertisement.
- **Estimated # of qualified responders/referrals from phone pre-screening 10%: (252):** This factor is based on expectations that 1 out of every 10 callers will be a potential patient presenting with symptoms and medical history that meet pre-screening criteria.
- **Estimated # attending site screening 85%: (214):** Of the patients who pass the telephone screening an estimated 85% will attend the screening appointment at the clinical research site.
- **Estimated # of screen failures 50%: (107):** Abbott has estimated that half of the patients who are screened by study sites will not qualify based on exclusion/inclusion criteria.
- **Number of randomized subjects: (107):** According to the screen failure rate provided by Abbott, we anticipate that half of the patients who are referred to a site will pass the screening visit and ultimately enroll in the trial.

Core Program Elements

Radio Advertising Campaign

The advertising period would be January through March 2000 with creative development, IRB approval process, media planning and study site relations beginning immediately upon Abbott's approval to move forward.

The media strategy is to utilize radio to effectively reach the defined target audience (see below) using specific programming. Radio has been selected because of its sense of urgency, high frequency message exposure, affordable, efficient geographic coverage of the current study site list, and ability to target the audience through station format selection.

Strategic format selection is a key component in the success of a patient recruitment campaign. News and talk formats will be utilized for several reasons:

- Services well the target demographic
- Possesses active listenership – foreground, not background
- Typically yields an excellent patient response
- Feature health reports as part of their shows
- Well-known show hosts offer credibility to their sponsors

In addition, stations that play music, which appeals to the appropriate demographic audience, will be chosen to ensure effective targeting.

The media target audience for this recruitment program has been defined as:

- Adults age 50+ (with equal media weight given to men and women)
- Broad income category, but with a primary focus on those with fixed incomes or limited financial resources
- Some media weight will be applied to stations reaching English-speaking Hispanic and African American populations in relevant study markets, given diabetes prevalence

The media planning strategy includes the purchase of 15 spots per week on 2 stations for each study market for each broadcast week. However, please note that we are not recommending radio advertising for the Syosset, New York study site for the following reason: The target study population in and around Syosset will be listening to stations that cover the entire New York metro area. As New York is the one of the most expensive radio markets in the U.S., purchasing air time would not be expected to provide a meaningful return on investment unless there were multiple sites throughout the metro area – and only a very small portion of those reached by the ad will be willing to travel to Syosset.

Commercials will air Monday through Thursday only, when patient response is typically strongest. Spots will run primarily between the hours of 10 AM – 3 PM. Purchasing spots aired during specific programs during the morning and afternoon drive times may also be appropriate for some sites. It is recommended that the schedule run simultaneously for 4 weeks in each market separated by a 2-week hiatus. This hiatus allows study sites to follow-up on referrals and provides a more controlled referral volume so they will not feel so overwhelmed. However, depending on initial communications with the sites, this can be adjusted to fit their ability to process leads. During the hiatus weeks, Abbott/ Phone Screen/ GCI Team will evaluate the productivity of the first ad weeks.

Core Program Elements – continued

The radio ad script will be written to help potential study candidates, their spouses or significant others, self identify. It will utilize a strong call-to-action, and all ads will carry a single toll-free number. We expect that even with targeted messages and media planning that there will be a significant number of disqualified callers, due to the rigors of the protocol. Sites will be advised that referrals generated through advertising are potential “leads” and that the purpose of the centralized telephone screening is to weed out those who are obviously inappropriate (e.g. inappropriate symptoms or medical history) for the study.

Implementation Logistics:

- Develop a 60 second radio script for approval by Abbott and the central and local IRBs
- Oversee production and distribution of the radio spot
- Direct media planning
- Collaborate with Phone Screen on Call Center Activities and Reporting
- Communicate with sites to announce media plans in their local markets

Tentative Tier One (highest priority) markets for radio advertising include:

- | | |
|--|-------------------------------|
| • Fort Lauderdale, Pembroke Pines, and | • Minneapolis |
| • Miami/ Boca Raton | • Phoenix, Peoria |
| • Atlanta | • San Francisco, Walnut Creek |
| • Clearwater | • St. Louis |
| • Fort Myers | |
| • Houston | |

Tentative Tier Two markets include:

- | | |
|---------------|-----------|
| • Albany | • Hershey |
| • Albuquerque | • Norfolk |
| • Buffalo | |

Tentative Tier Three markets include:

- | | |
|-------------------------|---------------|
| • Altoona, Duncansville | • Madison |
| • Dinuba | • Providence |
| • Greenville | • Springfield |
| • Little Rock | |

Centralized Call Center

The centralized call center is the locus of all patient response activity. It removes the burden of pre-screening potential volunteers from the study site personnel and provides referral services to the study sites. The call center accepts and screens all calls made to the study specific toll-free number in response to recruitment advertising. The call center will track specific recruitment matrix and provide referrals directly to the study sites.

- **Call Center Set-up:** Phone Screen project team will design and establish customized systems for call processing. These systems include call guide development and programming, toll free number(s) acquisition and set up, and programming of clinical research site contact and location information.
- **Live Operator Service:** Phone Screen's patient recruitment specialists will be available to speak with patients "live" from 7am – 10pm central standard time. Aided by a computerized call guide, Recruitment Specialists screen callers according to the protocol inclusion-exclusion criteria. Calls received after hours (10:01pm- 6: 59am) will be captured by a study-specific voice mail and followed up on the next business day.
- **Project Management:** Phone Screen provides project coordination and staffing services, manages data management systems, data storage, back up, and document management. A project team will be formed to ensure timely and thorough responses to the needs of the project partners. Key staff involved in Project Management includes:
 - **Project Manager:** Day-to-day management of the project and project team.
 - **Project Assistant:** Administrative support including data entry and report processing.
 - **Shift Supervisors:** 24-hour supervision of Recruitment Specialists.
- **Training:** Phone Screen and GCI will schedule a specialized training program for all recruitment specialists who will service the PDN study. The training program will include a review of: diabetes and PDN, study protocol, inclusion/exclusion criteria, screening questionnaire, likely callers, handling difficult callers, frequently asked questions, and referral procedures. The Abbott Team will be invited to participate in the training.

Reports

Reports provided by Phone Screen will be used to provide sites with detailed patient information, track patients through the enrollment process and summarize critical study data. Several report options are listed below. Customized reports are also available. SAMPLE REPORTS ARE ATTACHED.

- **Patient Screen:** Daily report detailing patient responses to screening questions and appointment times. A patient screen report for each pre-qualified caller will be faxed or e-mailed to the appropriate research site (depending on site preference).
- **Referral Tracking Worksheet:** Weekly worksheet sent to research sites to obtain status of referred patients. Information is summarized to provide "lag time to 1st appointment" management reports.
- **Management Reports:** Periodic and cumulative summaries of key recruitment statistics that are provided at regular intervals or on an as needed basis. These reports help to inform recruitment and retention management decisions. Samples reports are provided in the Appendix section.

Optional Supplementary Programs

Direct Mail Campaign

Well-designed, strategically targeted direct mail campaigns are a proven means of encouraging consumer response. A direct mail campaign targeting individuals 50 and older already diagnosed with diabetes will reach approximately 123,000 people in and around the counties in which there are clinical trial sites. By targeting this selected demographic, we can more efficiently and cost effectively reach potential trial participants.

A compelling direct mail piece can anticipate and address the most commonly asked questions about the research being conducted and emphasizes the benefits of participating in the trial, as well as providing customized information on individual sites. In addition, the piece can provide the option of calling the study 800 number or responding directly to the study site via a reply card. If the latter option is chosen, the study coordinator will contact the patient directly for follow-up and further screening.

Benefits

- A targeted approach will save time and money in reaching the most promising candidates for the study
- Written materials provide an opportunity to reinforce key messages about the study
- Response to the mailing is measurable
- Immediate response facilitates accelerated screening and enrollment

Implementation Logistics

- Rent/buy appropriate lists of self-reported diabetics over 50-years-old
- Design and write a generic piece which will be customized to each market
- Provide a perforated reply card
- Facilitate central and local IRB review and approval
- Manage printing and mailing of the piece
- Evaluate success via ongoing communications with study sites and tracking calls to the 800-number generated by the direct mail piece

Physician Referral Expansion Pilot Program

GCI will provide and manage the services of a partner organization with expertise in generating physician referrals. We will identify five sites to participate in a pilot program and systematically review processes for encouraging referrals. Through interviews with investigators and coordinators and reviews of patient, medical center, clinic and hospital databases, we will identify physicians relevant to the study and determine areas for improvement in dealing with them. Based on the findings, we will develop and implement an action plan for accelerating and enhancing the enrollment process. Based on the level of success and timing, we may wish to expand this program to additional markets.

Benefits

- Physician referrals offer a targeted, efficient approach to identifying patients who meet very specific inclusion/exclusion criteria for study

Implementation Logistics

- Identify pilot sites, which would benefit most from a referral network

- Conduct and analyze site-by-site review of current "referral generating" practices and impact of "medical political" climate and dynamics.
- Mine site's internal and external medical community for physicians relevant to the study referral (via databases for medical centers, hospitals and larger clinics)
- Collaborate with local investigator and study coordinator to identify viable referral sources.
- Implement market-specific physician referral generation program including
- face-to-face meetings with potential referring physicians, written materials and ongoing contact to keep study "top of mind."

Study Site and IRB Relations

GCI recommends an overall strategy of responsive partnership with the study sites. GCI will implement this strategy through direct interaction with site personnel on a regular basis, once the centralized program is launched. A site database will be created and maintained by Phone Screen and GCI.

Benefits

- Enhanced relationships with site coordinators and investigators may increase their interest/commitment to Abbott trials over those of competitors
- Additional support for site coordinators and investigators may serve as an incentive to take on more patients

Implementation Logistics

- Contact all study site investigators (in writing only) and coordinators (by telephone and in writing) to introduce the GCI Healthcare Site Relations Manager, the recruitment support program being planned by Abbott and GCI, and review program procedures and responsibilities for the site
- Assess site's experience with and receptivity to centralized recruitment programs, referral call back capabilities and obtain local recruitment suggestions from coordinator/investigator
- Maintain ongoing contact with site coordinator during program implementation to inform of advertising plans, assess progress, referral tracking, etc. Document important conversations on Site Relations Tracking Worksheet
- Submit radio script, call guide and FAQ documents to central IRBs and sites with local IRBs for review and approval
- Track receipt of IRB approvals; notify call center of approval and activate advertising in specific market
- Conduct periodic teleconference calls with sites to assess recruitment program progress, enrollment status, etc.
- Inform Abbott of "critical" site issues relevant to recruitment program that emerge
- Provide Abbott with copies of site correspondence for investigator files

###

McCarthy Deposition Exhibit 21

P's Exhibit DH

November 2000 ABT-594 Project Status Report

Monthly Highlights

- In-life phase of 2-year mouse carcinogenicity studies completed mid-November.
- Proposals and timelines from 3 patient recruitment firms were reviewed, with a conclusion reached that hiring a recruitment firm to increase enrollment for study M99-114 was not a viable option at this time.
- USAN approval for the generic / chemical name for ABT-594 was received. The United States Adopted Name for ABT-594 (A-166594.47) is ebanicline tosylate (e-ban-ki-len to-se-lat).
- Preliminary commercial capsule design selected by AI and PPD Marketing, with input from across the project team. The primary parameters are: Size 3 hard gelatin capsules, 2 strengths / colors: 75 mcg - 1/2 light yellow, 1/2 white, 150 mcg - both halves light yellow, printed with strength and trade name (TBD.)

Key Progress Gauges - November Accomplishments	Target Date	Status
• Final decision on commercial capsule parameters to be provided by NPD to PARC	11/10	Complete - All information provided by 11/13.
• Achieve enrollment of at least 220 patients in M99-114 by 11/30	11/30	Complete - 246 patients enrolled as of 11/30
• Complete 7 "good will" site visits for M99-114	11/30	Complete
December Projections		
• Portfolio analysis team review of forecast and expense projections	12/19	
• Achieve enrollment of at least 260 patients in M99-114 by 12/31	12/31	

1 of 6

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EXHIBIT
21
McCarthy
9-29-01a2b

November 2000
ABT-594 Project Status Report

Project Cost Summary - November

\$000's	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	22.9	7.0	7.6	7.9	.3	157.1
CMC (PARC & SPD)	13.0	3.0	3.2	2.6	-.6	27.6
Drug Safety	8.7	2.8	3.0	2.4	-.6	18.3
Other Support Costs	0.7	.5	.6	1.5	.9	12.2
Total	50.5	13.3	14.4	14.4	0.0	215.2

File NDA = 9/2/2003

Protocol # - Study Name	Clinical Study Progress	Total R/OSS \$000	Total Target Patients	Current Enrollment
M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	Start (1st Patient Dosed) 04/00 End (Last CRF in House) 04/01	3,000	320	246 (as of 11/30)

3 of 6

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Business Rationale

Date: November 2000
 Franchisee: Neuroscience
 Venture: Analgesia

November 2000
ABT-594 Project Status Report

ABT #: ABT-594
 Trade & Generic Name: TBD, ebanolone tosylate
 Mechanism of Action: Neuronal Nicotinic Receptor (NNR) Agonist

Indications: Neuropathic Pain
 Chronic Pain (publication only)

Product Profile

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Not scheduled	12/1996	High	100%	High
Chronic nociceptive pain efficacy	10/1998	Medium	2001	High
Neuropathic pain claim	6/1999	Medium	2001	High
General pain claim	12/1996	N/A	N/A	High
Moderate to moderately severe pain	5/1998	Medium	100%	High
No tolerance/dependence or withdrawal	5/1998	High	2001	High
Very few abnormal LFTs	6/1999	Medium	2001	High
Low nausea/vomiting at effective dose	5/1998	Medium	2001/100%	High
Other safety OK	5/1998	High	2001/100%	High
No differential efficacy (nicotinic users vs. non users)	5/1998	Medium	2001/100%	High
No differential side effect profile (nicotinic users vs. non users)	5/1998	Medium	2001/100%	Medium
No inhibition of cravings in ex-nicotine users	6/1999	Low	400%	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	High	2001	High
12/1896	High	100%	Medium	
9/1999	High	100%	High	

Probability Key:
 High = 70-100%
 Medium = 30-69%
 Low = 0-29%

Market Forecast

Parameter	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
Patent Status:	12/1999 (acute)	12/2001	9/2003
MDA Filing:	6/2001 (chronic)	12/2003 - Eur	9/2004
Ex-U.S. Filings:	N/A - Jpn	12/2003 - Jpn	9/2004
Projected U.S. Launch:	12/2001 (acute)	6/2003	9/2004
Projected ex-U.S. Launches:	12/2002 (chronic)	12/2003 - Eur	9/2004
Same as above - Eur	N/A - Jpn	9/2004	9/2004
Peak TRx Share, U.S.:	6.8% (patients)	5% (Rx)	10% (Neuropathic pain)
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	10% (Persistent Chronic Pain)
Peak Sales, U.S.:	\$285	\$518	same as US assumptions
Peak Sales, ex-U.S.:	\$308	\$310	\$466
Pre-Tax NPV @ 15%, ex-U.S.:	\$338	\$305	\$359
After-Tax NPV @ 12.5%, U.S.:	\$412	\$813	\$296
Avg daily dose	50 mg	200 mcg	150 mcg
Target Drug Costing at Launch	\$2,500	\$2,500	\$40,000 (base eq.)
SMM at Launch	94.8%	97.2%	98.6%
SMM at Year 5			

* Forecast based on general pain target indication
 ** Forecast based on neuropathic pain indication and published study in chronic pain

4 of 6

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Project Overview

November 2000
ABT-594 Project Status Report

Metrics Dates

Description	Date
DDC Meeting	12/1996 (PPCC)
Start of first GLP animal tox study	2/1997
First dose in human (dog, Phase I)	7/1997
First dose in patient (dog, Phase II)	7/1998
First dose in Phase III	2/2002 (est.)
Last Patient/Last Visit	4/2003 (est.)
NDA Filing	9/2003 (est.)
NDA Approval	9/2004 (est.)
Europe (EMEA) Filing	9/2003 (est.)
Europe (EMEA) Approval	TBD
Japan Filing	4/2004 (est.)
Japan Approval	TBD

SPD

Drug Substance	Plan	Actual Date	Plan 6/1999 Projected Costing*
Source/Lot #	6/1999		
D-4SL	0.3 KG	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (Tox/late Sal)

PARO

Activity	Plan	Current	Actual
6/1999	Revised	10/00	
Phase I / Formulation (PIB)	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped (osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
Phase IIb / Formulation (HCC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lot(s) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

* Performed by IDC

Toxicology

Toxicology Activity	Plan Start	Actual Start	Report
1999	1999	Date	Completed
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	..	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Cardiogenicity (2 yr) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr) Mouse	12/1998	11/1998	Ongoing

5 of 6

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November 2000
ABT-594 Project Status Report

Clinical Study Progress

Protocol:

M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective:

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses:

150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses:

Placebo

Target Enrollment:

320

Target Cost:

\$3 MM

Actual Cost:

TBD

Status:

Ongoing - 246 patients randomized as of 11/30

Major Findings:

TBD

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6 of 6

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McCarthy Deposition Exhibit 22

P's Exhibit DL

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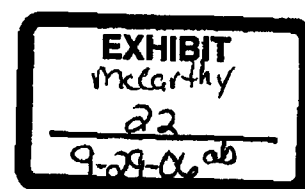
ABT-594

Descriptive Memorandum

November 2000

Abbott Laboratories

Highly Confidential



ABBT144600.UR

ABT-594 Opportunity Overview

ABT-594 is a non-opioid, non-NSAID analgesic that is a potent and selective neuronal nicotinic receptor (NNR) agonist being studied for the treatment of pain. ABT-594 is 30 to 100-fold more potent and equally efficacious to morphine in several well-characterized animal models of pain. The preclinical side effect and dependency liability profile of ABT-594 is superior to that of morphine.

ABT-594 is orally administered, and BID dosing is expected. Its initial targeted indication is symptomatic treatment of diabetic neuropathic pain. It is covered by a composition of matter patent through June of 2016, and also has a use patent pending in analgesia that would provide protection through September of 2017.

The IND filing of ABT-594 was in December 1998. A Phase IIb (dose ranging) trial began April 2000 in diabetic neuropathic pain. A Go/No Go decision for clinical efficacy is expected June 2001. The NDA filing is expected in 3Q2003. Development of additional formulations is under consideration (parenteral, transdermal, extended-release). Peak sales of ABT-594 are projected to reach over \$420MM in the US and \$362MM ex-US by 2008.

U.S. sales in 1999 for the key neuropathic pain treatments, Neurontin, carbamazepine, and tricyclic antidepressants (TCAs), are estimated to be \$350 million. Neurontin sales account for the bulk of this, with an estimated 40% of this antiepileptic drug's sales being for neuropathic pain. Neurontin's 2000 sales are expected to reach \$1 billion with perhaps 50% of its use in neuropathic pain. This dollar market value likely underestimates this market's potential due to a number of factors. Only the anticonvulsant, Tegretol (carbamazepine), currently off patent, and Lidoderm, a lidocaine patch, have specific indications for a type of neuropathic pain (trigeminal neuralgia and post-herpetic neuralgia, respectively) in the U.S. Outside the U.S., Neurontin recently received an indication in the U.K. for the treatment of neuropathic pain. Despite these opportunities, there has been little to no funding from the pharmaceutical industry to improve diagnosis and treatment of neuropathic pain and drive market growth. Of even greater impact on total market sales, most of the agents used to treat this population, with this exception of Neurontin, are low-cost, generic products.

Ex-U.S. sales of carbamazepine and Neurontin for treatment of neuropathic pain are estimated to be approximately \$140MM in 1999. Carbamazepine is still the treatment of choice ex-U.S., with estimated sales of approximately \$90MM in neuropathic pain. Neurontin has achieved only \$53MM in sales for this pain segment, with a price approximately 3-4 times that of carbamazepine, suggesting a patient share of only 10-20%.

Nociceptive pain is categorized by duration (acute or chronic) and by severity (mild, moderate, and severe). The mild and, to a lesser extent, moderate segments have multiple product entries and are generally well satisfied by OTC products such as aspirin, acetaminophen and ibuprofen. The prescription market for nociceptive pain is made up of four key classes of analgesics: NSAIDs, COX-2s, Opioids (and combination products), and Other Non-Opioids. In 1999, sales for these four classes of analgesics exceeded \$12BB (\$6.7BB U.S., \$5.6BB Ex-U.S.)

Market Size / Prevalence

Pain is the most common symptom of disease and the most frequent complaint with which patients present to physicians. Chronic pain, including both neuropathic and nociceptive pain, is considered to be the single most common cause of suffering and disability in the industrialized world with an estimated 25-30% of the population experiencing some form of chronic pain.

Neuropathic pain is a frequent sequela of diabetes, cancer, AIDS and other viral infections, as well as entrapment neuropathies such as carpal tunnel syndrome. Diabetes and its associated complications are increasing at an alarming rate in the United States. Despite advances in treatment, the development of diabetic complications such as neuropathy remains significant. The diagnosed prevalence of diabetic neuropathy is estimated to be about 2 to 3 million patients, with at least 10 to 20% of those patients experiencing painful symptoms (~200,000 to 600,000.) AIDS-related neuropathic pain is estimated to affect approximately 40% of HIV-infected individuals (~14 million.) Post-herpetic neuralgia (PHN) is another virally induced neuropathic pain syndrome. Annually, acute herpes zoster infection (shingles) occurs in almost a quarter of a million people over the age of 60 in the U.S. alone. Pain lasting more than one year has been reported in 22% of patients over the age of 55 and in 48% of those over 70 years of age. In cancer, nerves can be damaged by mechanical distortion from a tumor mass, infiltration by tumor, chemotherapy, or radiation therapy and, therefore, neuropathic pain is common. An estimate of the prevalence rate for cancer-related neuropathic pain in the U.S. is 200,000 people.

Chronic nociceptive pain categories include osteoarthritis (OA), chronic back and neck pain, rheumatoid arthritis (RA), and cancer pain. These diagnoses are expected to become more prevalent as the population ages. Current overall prevalence for these disorders is staggering (over 200 million worldwide) and, although the diagnosed and treated populations are lower, improved treatment options and awareness have the potential to drive significant growth. OA is one of the most common nociceptive pain conditions treated by primary care physicians and three-fourths of OA sufferers surveyed indicate that the disease interferes with their daily activities. Chronic back and neck pain are also highly prevalent and represent an estimated 40% of a primary care physician's (PCP's) chronic pain patient population.

Competition, Current Marketed Products:

The following tables show the factored U.S. and ex-U.S. prescription and sales volume for key neuropathic pain therapies in 1999.

1999 Key Neuropathic Pain Products, Estimated TRxs				
Product/Class	1999 U.S. TRx (MM)	U.S. TRx CAGR '97-'99	1999 ex-U.S. TRx (MM)	ex-U.S. TRx CAGR '97-'99
Neurontin	3.3	26.3%	N/A	N/A
carbamazepine	1.0	12.6%	N/A	N/A
TCAs	8.2	1.1%	N/A	N/A
TOTAL	12.5	5.6%	N/A	N/A
Source: IMS, factored for neuropathic uses.				
N/A = not available				

1999 Key Neuropathic Pain Products, Estimated \$ Sales				
Product/Class	1999 U.S. Sales (\$MM)	U.S. Sales CAGR '97-'99	1999 ex-U.S. Sales (\$MM)	ex-U.S. Sales CAGR '97-'99
Neurontin	\$308	28.7%	\$53	57.6%
carbamazepine	\$17	13.1%	\$87	2.5%
TCAs	\$26	-3.3%	N/A	N/A
TOTAL	\$351	21.7%	\$140	10.1%
Source: IMS, factored for neuropathic uses; Ex-U.S. data includes retail pharmacy data from all audited markets				
N/A = not available				

Competition, Products In Development

Almost 100 compounds are currently in development for prescription pain management, though some of these compounds are also being developed for non-analgesic indications. Most of the analgesic compounds in the pipeline represent incremental improvements over the opioids or NSAIDs, or consist of new formulations or delivery mechanisms for the standard analgesics. Fewer than 30% of the compounds in development have novel mechanisms of action. Drugs with novel mechanisms are expected to provide the bulk of promoted competition for ABT-594.

In addition to the novel analgesics in the table below, a number of new formulation and combination products, most often containing an opioid, are in development. Second generation COX-2s are also in development but are not likely to represent major breakthroughs on the scale of the first generation products.

Analgesia Development Pipeline – Key Novel Agents				
Product	Company	Mechanism	Phase	Comments
pregabalin	Pfizer	Unknown; possibly through $\alpha 2$ subunit binding	III	Neuropathic pain; chronic pain, follow-up to Neurontin
saredutant	Sanofi	NK-2 receptor antagonist	II	General pain; MOA losing favor; active program
ZD4952, ZD 6416	Zeneca	Prostaglandin receptor antagonist	II	Moderate to severe pain, neurogenic pain
GV196771	Glaxo	Glycine antagonist	II	Chronic pain; showing promise
Tepoxalin	Johnson & Johnson	COX/5-LO inhibitor	II	OA, described as 'steroid replacing anti-inflammatory drug'
darbufelone	Parke-Davis	COX/5-LO inhibitor	II	General pain
117mSn DTPA	Brookhaven National Lab/Diatide	Unknown	II	Cancer pain Bone cancer (preclinical)
cizolirtine	Esteve	Substance P agonist	II	Analgesia, antipyretic
ADD 234037/harkoseride	Houston University	Glycine NMDA associated antagonist	II	Neurogenic pain
LY303870/lanepitant	Eli Lilly	Neurokinin 1 antagonist	II	Pain (migraine – discontinued)
colykade devacade	Merck	Cholecystokinin B antagonists	II	Pain (UK)
RPR 100893 dapitant	Aventis	Neurokinin 1 antagonist	II	Pain (France)
prosaptide TX14A	Myelos Neurosciences	Unknown	I/II	Diabetic neuropathies, Pain
CNS 5161	Cambridge NeuroScience	Glutamate antagonist, NMDA receptor antagonist	I	Neurogenic pain
HCT-3012	NicOx	Nitric oxide NSAID	I	Pain and inflammation
Sources: ADIS, IMS, Decision Resources, company reports				

Analgesia Development Pipeline – Nicotinic Mechanisms			
Product	Company	Phase	Comments
GTS-21	Taisho	II	Target is Alzheimer's disease; may have preclinical pain program; looking for partner
CMI 980	Cytomed	Preclinical	Target is pain; epibatidine analog
SIB-T1887	Sibia	Preclinical	Target is pain
FID 072021	Fidia	Preclinical	Target is pain; not actively funding
Sources: ADIS, IMS, company reports			

Unmet Needs

In general, a significant unmet need exists for safer, non-abusable, non-addicting, non-tolerance-producing, and non-scheduled efficacious oral and parenteral analgesic products for the treatment of moderate to severe neuropathic and chronic nociceptive pain.

Unmet Market Needs and the Impact of the Pipeline	
Unmet Need	Pipeline Impact
Efficacy in moderate to severe pain without tolerance, dependence or abuse potential	Novel nicotinic agents like ABT-594 may provide efficacy in more severe pain states without opioid-like liabilities.
Efficacy in neuropathic pain	Pregabalin may provide incremental improvement in neuropathic pain efficacy over gabapentin, but may also have increased frequency of adverse events. Novel nicotinic agents like ABT-594 appear to have efficacy in neuropathic pain, based on animal models.
Reduction in the GI bleeding risk of NSAIDs	COX-2 inhibitors appear to reduce the incidence and severity of GI ulcers and bleeding; second generation COX-2s may increase therapeutic window further; ABT-594 may need to demonstrate low G.I. complication rate.
Overcome ceiling effect of NSAIDs	Preclinical studies did not indicate a ceiling effect for novel nicotinic agents like ABT-594.
Extended dosage intervals or novel delivery mechanisms for improved compliance and convenience	Once weekly dosing formulations being explored for COX-2s, etc. Transdermal patch technology improvements likely; may need to provide line-extension / alternate formulations for ABT-594.
Therapies aimed at disease modification, prevention	Agents that decrease rate of diabetic complications (e.g., aldose reductase inhibitors) or directly treat neuropathy (bimocromol) may decrease incidence of neuropathic pain; thereby decreasing available market for ABT-594.

Product / Development Background

Scientific Rationale for ABT-594

Recent findings in the understanding of pain mechanisms have led to new conceptual approaches to clinical pain and a new understanding of potential novel molecular targets for analgesic drug development. Molecular targets have included modulators of glutamate neurotransmission (NMDA antagonists), ion channel modulators (neuron specific calcium channels, TTX-resistant sodium channels), neurokinin antagonists (NK-1), and novel anti-epileptics targeting the calcium receptor. None of these approaches has yet produced compounds exhibiting broad-spectrum analgesic efficacy with decreased side effect liability.

ABT-594 is a non-opioid, non-NSAID analgesic that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of pain. The preclinical side effect and dependence liability profile of ABT-594 is superior to that of morphine. Mechanistically, ABT-594 is a potent and selective neuronal nicotinic receptor (NNR) agonist with high oral bioavailability in rat, dog, and monkey.

In pre-clinical studies, ABT-594 rapidly distributes to the brain following systemic administration and, like morphine, can work at multiple levels in the central and peripheral nervous system to modulate pain perception. ABT-594 produces antinociceptive effects by interacting at both central and peripheral nAChRs. Injections of ABT-594 into brain at doses 1000-fold lower than given peripherally produce marked antinociceptive activity, indicating that ABT-594 can also activate descending pathways from the CNS to modulate pain processing. It also inhibits the release of the primary nociceptive transmitters, substance P and calcitonin gene related peptide (CGRP) *in vitro*, at the level of the dorsal horn of the spinal cord suggesting that ABT-594 can attenuate mechanisms leading to neurogenic inflammation, central sensitization and consolidation of pain-mediated neuronal changes.

ABT-594 is expected to be a highly differentiated product. It is expected to be the first neuronal nicotinic receptor agonist to receive an indication for pain. It has a novel mechanism of action and a potentially broad coverage of chronic pain conditions. In addition, it has an opioid-like efficacy without tolerance, dependence or abuse potential, while having equivalent/superior efficacy to other drugs used to treat neuropathic pain.

Clinical Studies

Human clinical trials began in 1997. Phase I trials with an oral solution formulation indicated that 150ug/day would be the maximum tolerated dose. Results from subsequent phase I and phase II trials with soft elastic capsule (SEC) and hard gelatin capsule (HGC) suggest that higher doses would be tolerated. Phase IIa studies with ABT-594 SEC formulation suggest a trend towards analgesic effect at 75ug BID. ABT-594 was generally well tolerated in these studies. The most common adverse events for subjects receiving ABT-594 75ug BID were nausea (15%), headache (13%), dizziness (7%), insomnia (6%), and vomiting (5%).

A phase IIb study for neuropathic pain at higher, titrated doses of ABT-594 began in April 2000 and ends in June 2001. A total of 320 patients are anticipated to be included in the study.

Patent Status

A notice of allowance has been obtained from the United States Patent and Trademark Office on an application providing composition of matter coverage for a large class of structurally related neuronal nicotinic receptor analogs, which encompasses ABT-594 (5246.U.S.) The original filing date for this application dates back to October 9, 1992. The expiration of patent coverage for composition of matter for ABT-594 under this patent is June 2016.

An additional application (6013.US.01) which includes a use claim for ABT-594 species in analgesia was filed in September 1997, with subsequent divisional filing of ABT-594 species composition of matter. Despite this later composition of matter filing for the species claim, it is likely that a "terminal disclaimer" will be necessary that dates the composition of matter claim back to the original genus patent (5246.U.S.) We have paid the issue fee for this patent on July 19, 2000, and are anticipating the patent to issue 90 - 120 days from that date. If this patent is allowed, it will provide 20 years from date of filing for the use of ABT-594 in analgesia, which will extend the patent life of ABT-594 to September 2017.

The original application providing generic composition of matter coverage was filed broadly ex-U.S. (WO94/08992) and this application published on April 28, 1994. A second foreign filing (WO96/40682) published on December 19, 1996. These cases are all still pending.

As additional information regarding potential uses for ABT 594 is gathered, applications to expand the scope of ABT 594's patent will be submitted. A task force consisting of members of NUDR, the Analgesia Venture, New Product Development, the Neuroscience Franchise, and the Abbott Patent Department will conduct periodic review of the patent.

Considerations

Target Profile:

The current status of ABT-594's profile vs. target profile is summarized in the table below:

Target Profile Attribute	Probability
Not scheduled (DEA)	High
Very few abnormal Liver Function Tests	High
Few Drug interactions	High
BID / TID dosing	High
No reduced efficacy or increased AEs in nicotine users	High
Onset of action 1.5 – 2.0 hours	High
Neuropathic efficacy	Medium
No tolerance, dependence or withdrawal	Medium
Other safety OK	Medium
No cravings in ex-nicotine users	Medium
Low nausea / vomiting	Low

Label Strategy:

BASE: Indicated for the treatment of diabetic neuropathic pain.

- UPSIDE:
- 1) Treatment of pain associated with OA
 - 2) Treatment of post-herpetic neuralgia
 - 3) Treatment of neuropathic pain
 - 4) Treatment of chronic pain
 - 5) Treatment of cancer pain

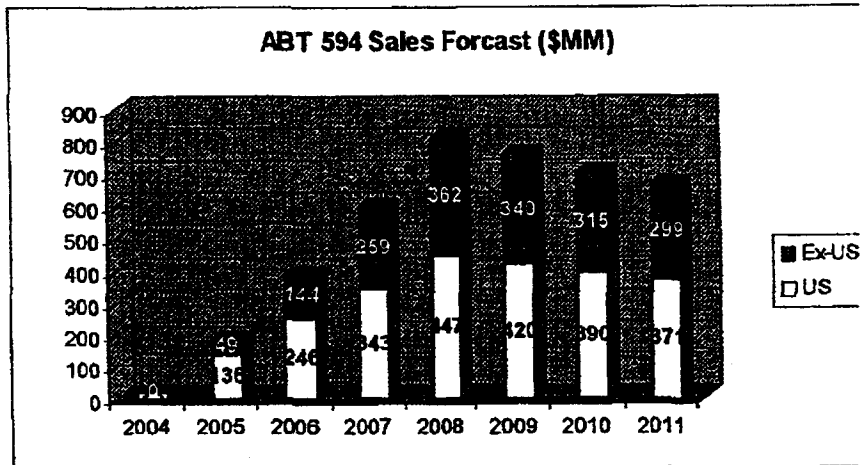
Cost of Goods Sold:

The projected average daily dose is expected to be a maximum of approximately 600 mcg base equivalent / day. Based upon this dosage projection and the estimated cost of bulk drug substance of \$40M per Kg base equivalent, the estimated cost for drug substance at launch will be approximately \$0.024 per day.

Pricing:

US: Pricing new, and particularly novel, products at a reasonable premium will likely continue to be the norm in the years leading up to the launch of ABT-594. Current forecast assumptions put the price of ABT-594 at a level comparable to Celebrex and Neurontin, grown at a modest 2% per year to launch year AWP of approximately \$95 for a 30 day prescription.

Ex-US: New pain medications must demonstrate a true advantage in efficacy and/or side effects to receive regulatory approval, especially by the European Medicines Evaluation Agency (EMA); assuming the target efficacy and tolerability profile of ABT-594 is achieved, ABT-594 would meet this requirement. Because ABT-594 may have application in both neuropathic and chronic nociceptive pain, the ex-U.S. pricing assumption for ABT-594 is comparable to COX-2 pricing. The current average price for COX-2's is approximately \$1.10 per day; however, this reflects a large percentage of sales in "free-pricing" countries, where COX-2s launched first, which tend to have higher than average prices. Therefore, the average ex-U.S. price for ABT-594 is assumed to be \$0.90/day.

Financial Projections**Key US forecast assumptions:**

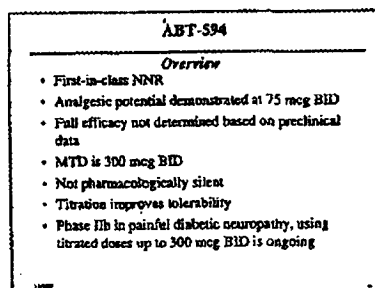
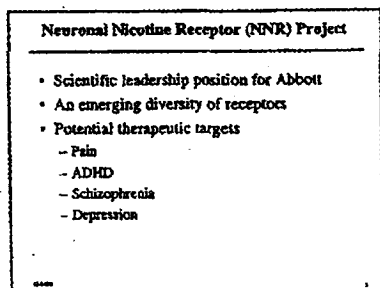
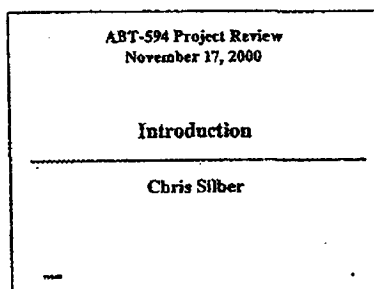
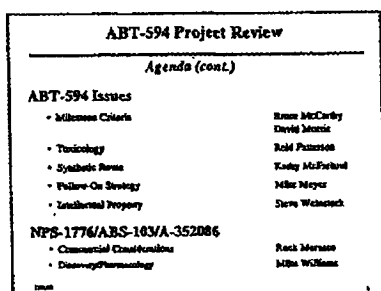
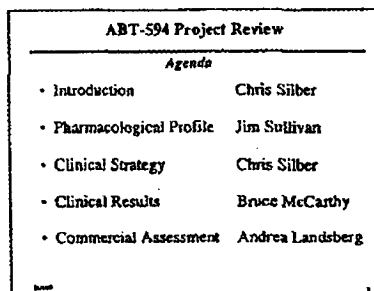
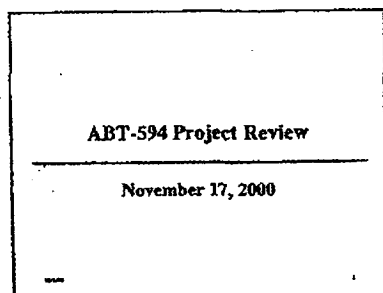
- First neuronal nicotinic receptor compound for pain to market
- Indicated for treatment of neuropathic pain; significant publication, or indication, from large scale trial on use in some form of chronic persistent nociceptive pain (e.g., OA) in 2006
- Efficacy greater than gabapentin in neuropathic pain and COX-2s in chronic nociceptive pain
- Good safety profile (no significant warnings or contraindications)
- Tolerability profile in line with other chronic pain products (CNS side effects improved over Neurontin and GI side effects improved over tramadol)
- No addictive potential
- Titration of 3-5 days
- Peak share 20% in neuropathic pain, 10% in chronic, persistent nociceptive pain (including off-label, 'spillover' prescriptions)
- Significant promotional and PR spend in early years
- Physician targets: D6-10 Neurologists, D3-10 Rheumatologists/Endocrinologists, D9-10 PCPs
- Sampling at 80% of details at launch, 5 units per detail, 7 days of therapy per unit
- Cost comparable to Neurontin and Celebrex
- Significant payor discounting
- Stocking at 8% of first year's sales
- Patent expires 12/2016

Additional Ex-US forecast assumptions:

- Same profile and peak share assumptions as U.S. forecast
- Price (ASP) = \$0.90 per day, or \$27 per 30 day Rx (comparable to COX-2 pricing)
- Average AI launch assumption is Q1 2005 to allow for additional regulatory filings (COFS and national filings in PAA and LA) and/or pricing negotiations (most markets in Europe) required in AI markets

McCarthy Deposition Exhibit 25

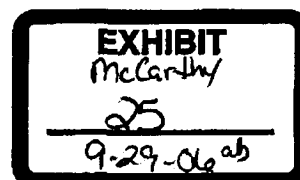
P's Exhibit DP



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ABBT 0019102

1



Pain Prevalence

- 22% primary care patients worldwide have persistent pain¹
- Neuropathic Pain
 - 20% of diabetics²
 - 40% of HIV infected
 - 36% of cancer patients

¹ most of the time, ≥ 6 months yr, WHO, 1998, JAMA
² at 10 years, Portenou, et al, 1995 NEJM

Pain Therapeutics Market

- \$12 billion in 1999 prescription sales of key classes (NSAID's, COX-2's, opioids, non-opioids)
- \$500 million in 1999 prescription sales of key neuropathic pain compounds (gabapentin, carbamazepine, TCA's)
 - use largely off-label
 - low cost generics

Neuronal Nicotinic Receptors

Analgesia Overview

- Nicotine produces analgesia in animal models of pain
- Discovery of epibatidine
 - South American tree frog
 - 200X more potent than morphine
 - Non-opioid
 - Epibatidine is a potent nAChR agonist (1994)
- Epibatidine is non-selective and highly toxic
 - Motor impairment
 - Seizures
 - Hypertension

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ABT-594 Project Review
November 17, 2000

Pharmacological Profile

Jim Sullivan

ABT-594: Preclinical Pharmacology

- Overview of neuronal nicotinic acetylcholine receptors (NNRs)
- Rationale for NNRs and pain
 - Knockout, antisense and pharmacological validation
- In vitro and in vivo profile of ABT-594
 - Efficacy
 - Side Effects

Molecular Diversity of Neuronal Nicotinic Acetylcholine Receptors (NNRs)

- Molecular diversity (9 α subunits, 3 β subunits)

CNS PNS

Subtype-Selective NNR Modulators Have Potential in a Variety of Disease States

CNS PNS

NNRs and Pain: NNRs are Expressed in Pain Pathways

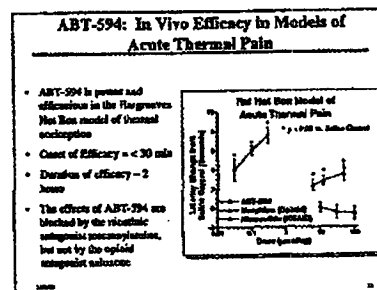
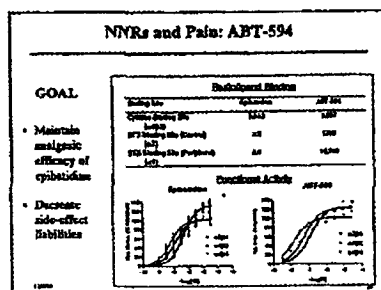
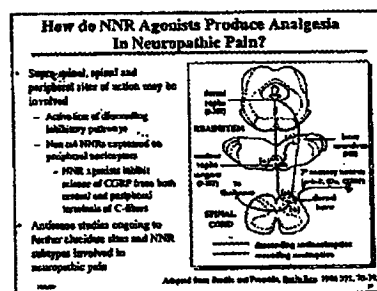
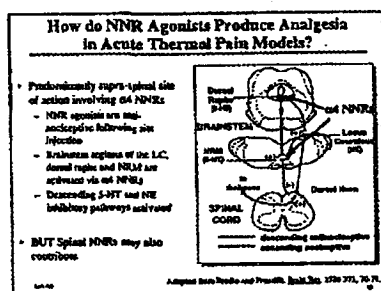
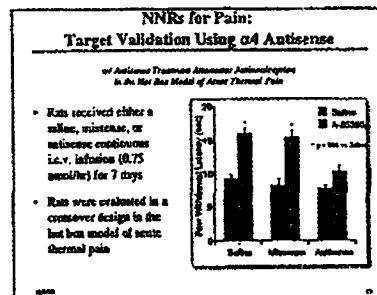
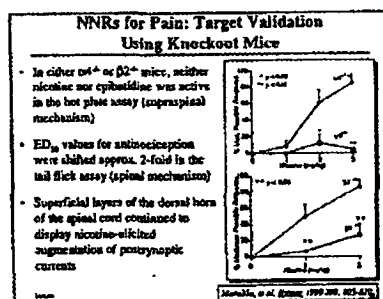
- CNS
 - $\alpha 4$ NNRs are localized on 5-HT neurons in NRM and dorsal raphe (Key CNS pain center)
- Spinal Cord
 - NNRs are expressed in dorsal horn neurons (Key spinal cord pain processing center)
- Sensory Neurons
 - $\alpha 3$, $\alpha 4$ NNRs localized to sensory neurons in DRG and in central and peripheral C-fiber nociceptors

Target Validation: NNR Agonists Are Analgesic

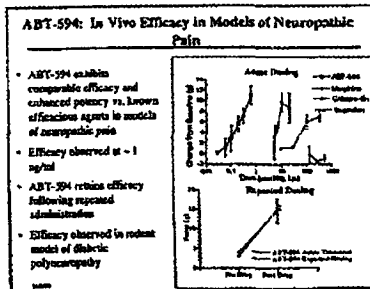
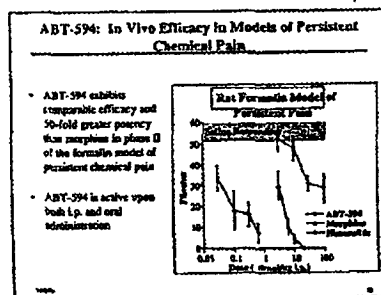
- NNR agonists are -
 - Antinociceptive (capable of causing nociceptive dysfunction in naive animals)
 - Antihyperalgesic (capable of reversing the increases in nociceptive sensitivity following injury)
- Nicotine analgesic in several models of pain
- Epibatidine (Key discovery)
 - 100x more potent than morphine
 - Non-opioid
 - Potent NNR agonist
 - BUT highly toxic

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CONFIDENTIAL

ABBT 0019105



ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain	Neuropathic Pain	Acute Nociceptive Pain	Anti-Inflammatory Activity
ABT-594	+++	+++	+++	0
Morphine	+++	+++	++	0
Tramadol	+++	+++	++	0
Meperidine	++	0	0	++
COX-2 Inhib.	+++	+++	+++	+++
Celecoxib	0	++	0+	0

+++ > 50-70% efficacy; ++ > 20-50% efficacy; + > 10-20% efficacy; 0 < 10% efficacy.

ABT-594: Preclinical Assessment of Side Effect Liabilities

- Assessment of "morphine-like" side effects
 - Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
 - Constipation
 - Respiratory Depression
 - Seizures
- Assessment of "nicotine-like" side effects
 - No effects on hemodynamics at plasma levels 10x higher than those required for efficacy
 - Effects on respiratory activity (dog vs. monkey)
 - Formal model exhibited no response to fully clonidine dose
 - Effects on spontaneous activity observed in awake alert state following acute administration
 - Effects observed following repeated administration
 - Effects on behavior, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing

ABT-594: Summary of Preclinical Findings

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NMDA and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
 - Constipation
 - Respiratory Depression
 - Seizures
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

ABT-594 Project Review
November 17, 2000

Clinical Strategy

Chris Silber

Broad-Spectrum, Non-Opioid Analgesic Activity by Selective Modulation of Neuronal Nicotinic Acetylcholine Receptors

A.W. BARNES, M. W. DECKER, M. W. HOLMES, P. CUNZOL,
D. DOWNEY-ROBERTS, P. S. FULLERMAN, R. S. BLISS, A. CLAZ,
A. M. DICKINSON, R. D. PERKIN, M. WILSON, S. P. ARNOLD

100-443887-100

ABT-594

Preclinical Pain Models

	Inflammatory Pain	Neuropathic Pain	Acute Neckspike Pain	Anti- Inflammatory Activity
AST-524	+++	+++	+++	0
Morphine	+++	+++	+++	0
Tramadol	+++	+++	+++	0
Buprenorphine	++	0	0	++
COX-2 Inhib. ++				++
Amiloriprilone 0				0

4-4 to 20% efficiency, 4-10 to 30-70% efficiency, 4-100% efficiency, 4-100% efficiency

ABT 594

Current vs DDC Profile

DEQ Trade (1997)	Current Policy (2000)
<ul style="list-style-type: none"> Indicated for the treatment of pulp (general pulp class) 	<ul style="list-style-type: none"> Indicated for the treatment of non-pulpable pulp. Affinity in GA demonstrated in non-sulfonated pulp
<ul style="list-style-type: none"> Improved safety profile compared to options including: <ul style="list-style-type: none"> low CE (metallic impurities) low respiratory depression low dermal potential no hepatotoxicity/renal toxicity 	<ul style="list-style-type: none"> In mouse in splash, no corneal or respiratory depression toxicity In DPM, potentially high DPM in concentrations near dose to vesiculating
<ul style="list-style-type: none"> No irritation 	<ul style="list-style-type: none"> Irritation on mucous EBs
<ul style="list-style-type: none"> Onset of vesicle in less than 30 minutes 	<ul style="list-style-type: none"> Onset of vesicle in 1.5 to 3 hours

ABT-594

Current Profile Status

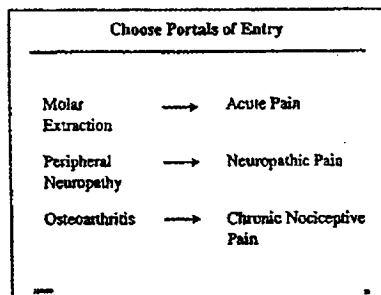
Attribute	Probability	Share Impact
Not scheduled	High	High
Very few scheduled LPTs	High	High
Few drug interventions	High	High
REDUCED Dosing	High	Medium
No reduced efficacy or increased AEs in nicotine users	High	Medium
Onset of action 1.5-2.0 hours	High	Medium
No tolerance, dependence, withdrawal	Medium	High
Other safety OK	Medium	High
No carryover to ex-nicotine users	Medium	Medium
Neuroprotective efficacy	Low	Medium
Low abuse/potential	Low	High

Spectrum of Activity: Where to Start?

Acute	Neuropathic	Chemical
Postherpetic surgery	Alcoholic polyneuropathy	Numbness
Median nerve entrapment	Diabetic polyneuropathy	Neuralgias
Acute heat pain	Ethanol polyneuropathy	Dysaesthesia
Tinnitus	Drug-induced polyneuropathy	Chemical back pain
Pharyngeal injury	Heavy intrathecal sensory analgesia	Arthralgic arthralgia
Post-herpetic surgery	Back pain	Cranial pain
Dysaesthesia	Cranial pain	Pharyngeal
Head pain	Tinnitus and arthralgia	Stiff neck disease
Shin pain	Post-herpetic neuropathy	Typhoid fever
Shin pain	Headache pain syndrome	Stiff neck
Parosmia	Spinal cord injury	Yersinia
Infection	Multiple sclerosis	Cranial visceral pain
	Complex regional pain syndrome (I, II)	
	Atypical facial pain	
	Shin pain	

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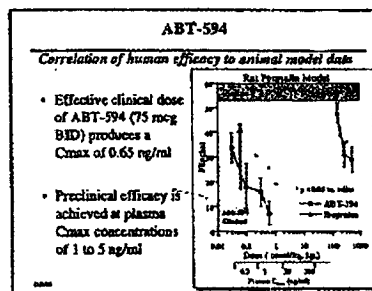
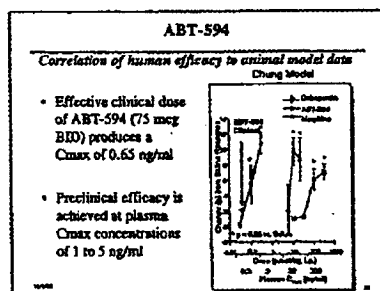
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ABT-594

Efficacy Conclusions

- Molar Extraction
 - Significance vs. placebo starting at 2 hours
- Neuropathic Pain
 - 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy
- Osteoarthritis Pain
 - 75 mcg BID may be lowest effective dose as judged by WOMAC scores



ABT-594

Current Label Target

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

Upside Claim	General Pain Claim
• OA Pain	• Not Viable due to 1.5 hour onset
• Post herpetic neuralgia	
• Neuropathic Pain	
• Chronic Pain	
• Cancer Pain	

ABT-594

Overview

- First-in-class NNR
- Analgesic potential demonstrated at 75 mcg BID
- Full efficacy not determined based on preclinical data
- MTD is 300 mcg BID
- Not pharmacologically silent
- Titration improves tolerability
- Phase IIb in painful diabetic neuropathy, using titrated doses up to 300 mcg BID is ongoing

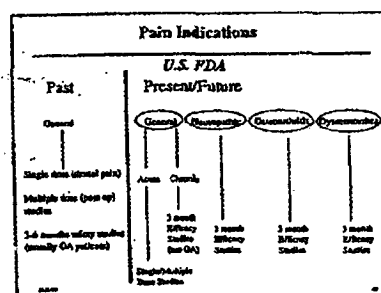
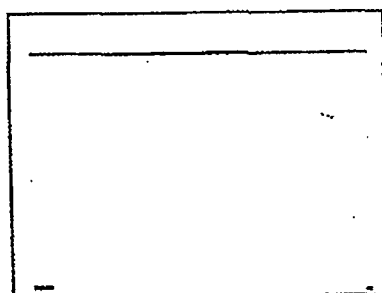
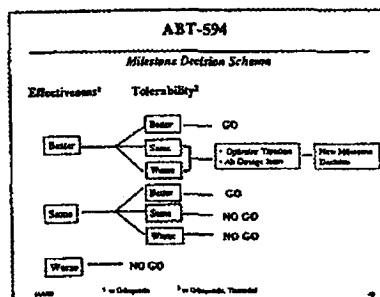
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ABT-594

Issues

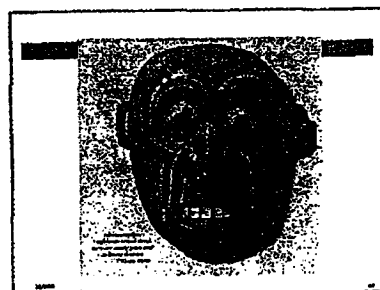
- Dropout rate in current Phase 2B study is about 30%
- Toxicology
 - Pre neoplastic lesions in rat 6 month tox study
 - Methylazir impurity has mutagenic potential
- Synthetic route modifications to be implemented
- Follow ons associated with limited IP risk



Backup

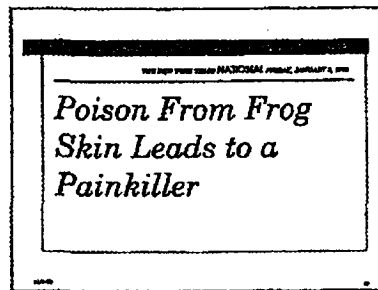
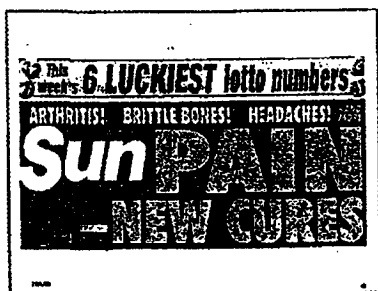
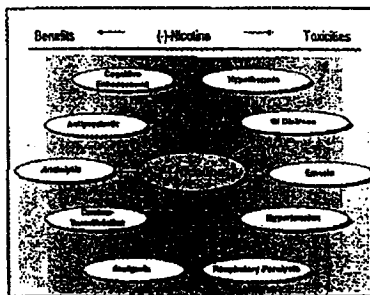
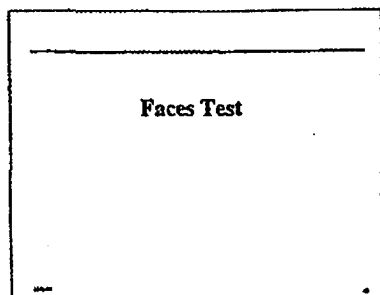
Clinical Strategy

Chris Silber



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ABT-594 Project Review
November 17, 2000

Clinical Results

Bruce McCarthy

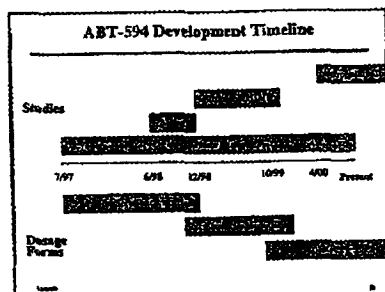
Lead slide take home message about ABT-594

ABT-594's analgesic potential demonstrated in:

Molar Extraction

Neuropathic Pain

Osteoarthritis



Phase II Overview

- Strategy
- Phase IIa Results
 - Dental, osteoarthritis, and neuropathic pain
 - Context: Currently Available Analgesics
- Phase IIb Status
- Go/No Go for ABT-594
 - NNR for pain implications

Strategy

What characterizes an innovative analgesic?

Spectrum of activity

Time of onset/duration

Level of efficacy

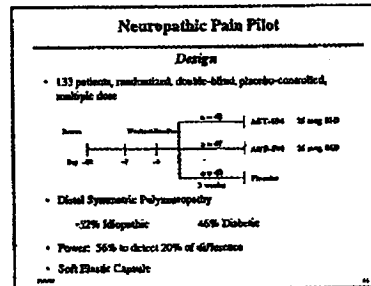
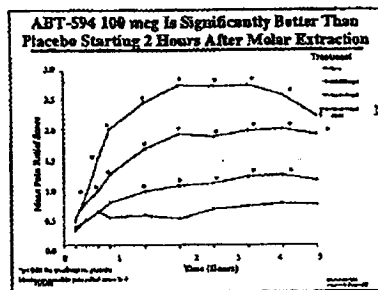
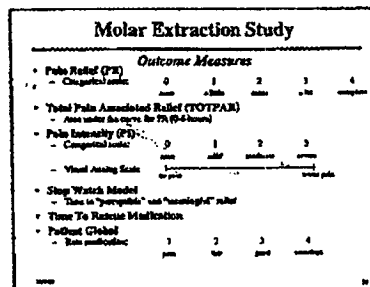
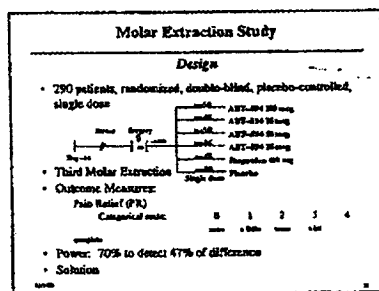
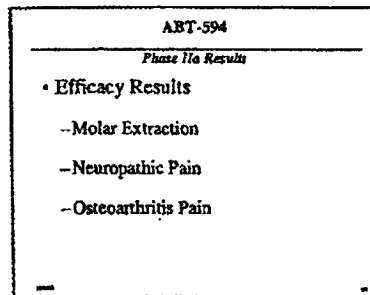
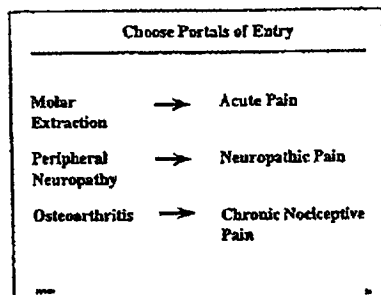
Safety/efficacy ratio

Spectrum of Activity: Where to Start?

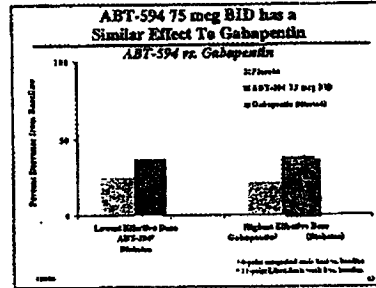
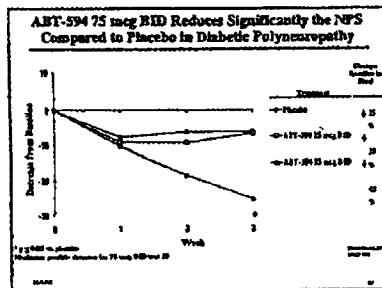
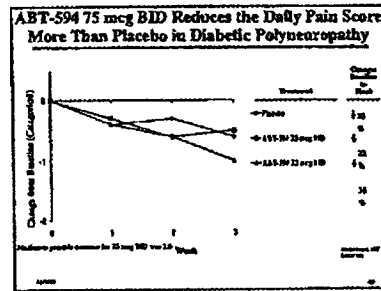
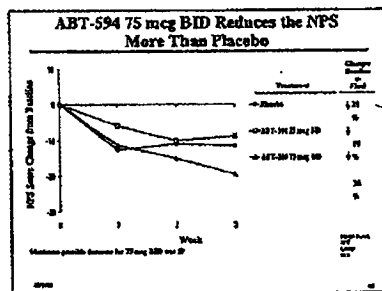
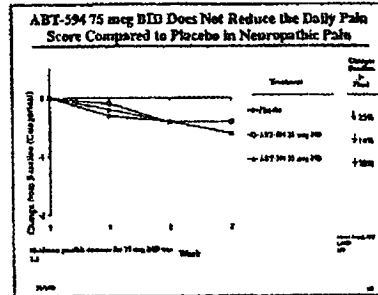
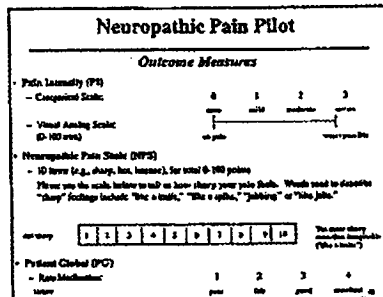
Acute	Neuropathic	Chronic
Post-dental surgery	Diabetic polyneuropathy	Osteoarthritis
Spinal cord injury	Idiopathic polyneuropathy	Chronic back pain
Acute heart pain	Alcoholic polyneuropathy	Rheumatoid arthritis
Trachea	Drug-induced	Cancer pain
Post-surgical surgery	HIV polyneuropathy	Fibromyalgia
Post-orthopedic surgery	HIV peripheral neuropathy	Stroke and disease
Dysmenorrhea	Secondary neuropathy	TMJ disorder
Small cell	Acute pain	Shingles
Biliary colic	Cancer pain	Yaws
Painful	Thyroidal neuropathy	Chronic visceral pain
Infection	Post-traumatic neuropathy	
	Thyroidal pain syndrome	
	Spinal cord injury	
	Multiple sclerosis	
	Complex regional pain syndrome (I, II)	
	Allyl alcohol pain	
	Phenylalanine pain	

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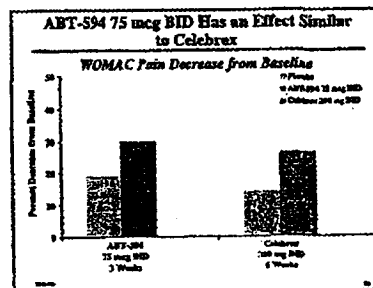
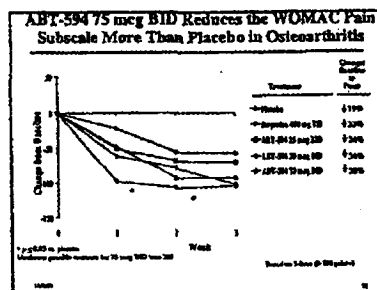
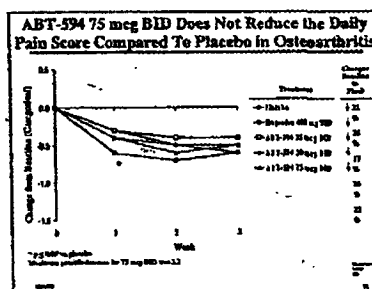
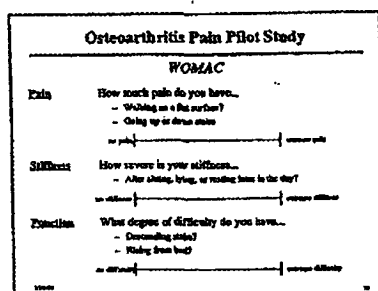
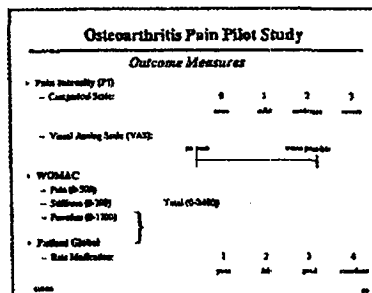
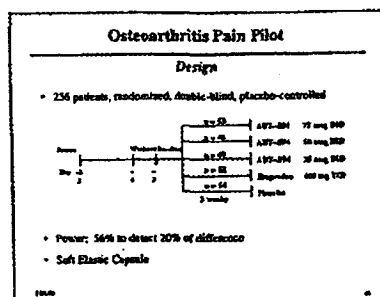
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Osteoarthritis WOMAC Benchmarks					
Percent Decrease from Baseline					
	Imipenem/ 400 mg TID	ABT-594 75 mg BID	Placebo/ 20 mg TID	Imipenem/ 400 mg TID	ABT-594 75 mg BID
Treatment	35 %	35 %	37 %	41 %	41 %
Placebo	35 %	35 %	—	35 %	35 %

¹ 11 weeks, N=1,100; WOMAC pain subscale used
² 11 weeks, WOMAC pain subscale used
³ 11 weeks, WOMAC pain subscale used
⁴ 11 weeks, WOMAC pain subscale used

ABT-594	
Phase IIa Efficacy Conclusions	
<ul style="list-style-type: none"> Analgesic Potential Demonstrated <ul style="list-style-type: none"> Molar Extraction <ul style="list-style-type: none"> Significance vs. placebo starting at 2 hours Neuropathic Pain <ul style="list-style-type: none"> 75 mg BID may be lowest effective dose for patients with painful diabetic polyneuropathy Osteoarthritis Pain <ul style="list-style-type: none"> 75 mg BID may be lowest effective dose as judged by WOMAC scores 	

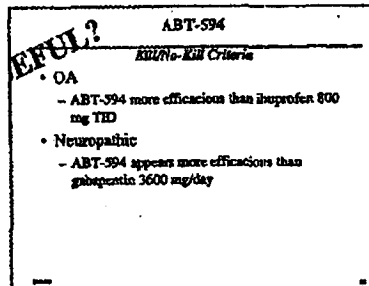
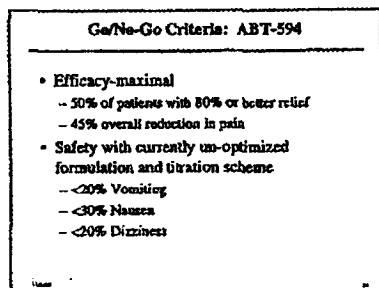
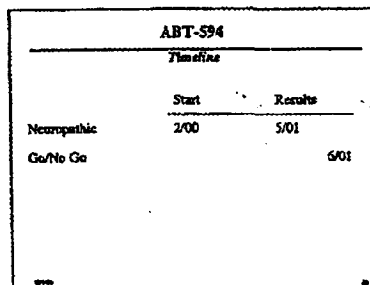
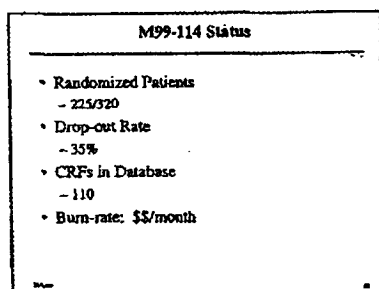
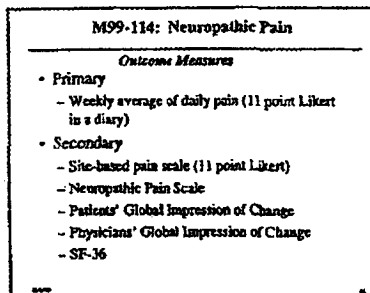
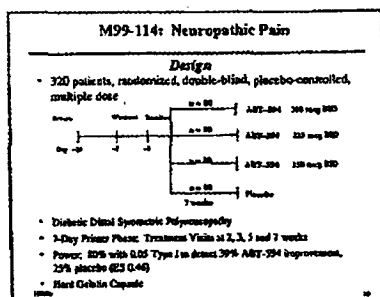
Tolerability Varies with Formulation				
Adverse Events				
	Molar Extraction 100 mg q 1 solution N=30		OA and Neuropathic 75 mg BID SEC N=30	
Event	Placebo	Placebo	Placebo	Placebo
Nausea	33 %	(17 %)	15 %	(0 %)
Vomiting	30 %	(7 %)	5 %	(0 %)
Dizziness	24 %	(4 %)	7 %	(0 %)

Adverse Event Rates for Select Analgesics				
	Celecoxib 300 mg qid	(N=100)	OxyContin [®] 30-100 mg q4-6 hr	ABT-594 75 mg BID
Confusion	8 %	NA	NA	0 %
Somnolence	23 %	NA	23 %	0 %
Dizziness	34 %	31 %	13 %	7 %
Nausea	8 %	34 %	23 %	15 %
Vomiting	NA	13 %	12 %	5 %
Constipation	NA	31 %	23 %	1 %

¹ Grade 1-2 adverse events only, up to 28 days
² NA = Not Available
³ "Controlled" study
⁴ NA = Not Available

ABT-594	
Phase IIa Conclusions	
<ul style="list-style-type: none"> Analgesic potential demonstrated Phase IIa studies included inadequate dose ranging <ul style="list-style-type: none"> SEC tolerated better than predicted by solution HGC tolerated in limited Phase I population to 300 mg BID fed Full analgesic potential will be defined with adequate dose ranging studies in Phase IIb 	

Phase IIb	
<ul style="list-style-type: none"> Trials <ul style="list-style-type: none"> Neuropathic Pain (M99-114) <ul style="list-style-type: none"> Ongoing Osteoarthritis Pain (M99-115) <ul style="list-style-type: none"> Initiated Doses <ul style="list-style-type: none"> 150, 225, 300 mg BID 	



Go/No-Go Criteria

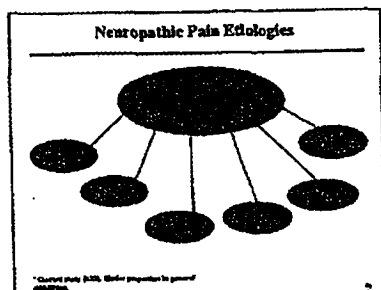
Implications for MNR Pharmacology

- Efficacy Criteria Met; Safety Unmet
 - Back-up compounds with improved therapeutic index in animal models
 - Nausea and vomiting more reliably separated than poorly testable outcomes like dizziness

Backup

Clinical Results

Bruce McCarthy



M99-114: Entry Criteria

- Greater than 18 years
- Painful distal symmetric diabetic polyneuropathy, stable for 3 months
- Average pain ≥ 4 during the baseline week by Pain Rating Scale (11-point Likert scale)
- Pain ≥ 4 at Baseline Visit by Pain Rating Scale
- No concomitant analgesics, except limited acetaminophen

M99-114: PK

- All subjects at Day 14 and Day 49
- Select subjects with complete profile at Day 14 and Day 49

Gabapentin Studies

Design

Gabapentin Studies	
Outcome Measures	
<ul style="list-style-type: none"> • Primary • Secondary 	

Gabapentin Studies	
Results	
<ul style="list-style-type: none"> • Primary • Secondary 	

Pregabalin Studies	
Design	

Pregabalin Studies	
Outcome Measures	
<ul style="list-style-type: none"> • Primary • Secondary 	

Pregabalin Studies	
Results	
<ul style="list-style-type: none"> • Primary • Secondary 	

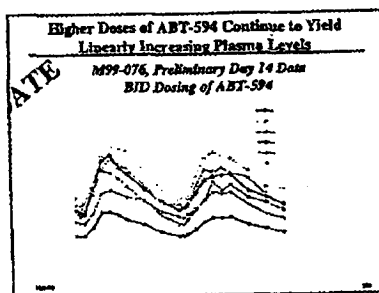
Gabapentin & Pregabalin	
Regulatory and Commercial Status	
<ul style="list-style-type: none"> • Gabapentin Approved for Neuropathic Pain in UK <ul style="list-style-type: none"> – Probable Mutual Recognition – Patent Life 13 more years • Pregabalin Submission 4Q00 <ul style="list-style-type: none"> – Neuropathic pain, epilepsy?, other pain?, psych? 	

FDA & Pain Drug Development

- Who?
 - McCormick
 - Hyde
 - Divisions
- Public Information
 - in transition
 - "General", "Acute", "Chronic", Disease-specific
- Discussions with Abbott

Anti-Epileptic Drugs for Neuropathic Pain

Status of Trials



Although NSAIDs and COX-2 Drugs Have Much Better Short Term Tolerability Profiles Than ABT-594, GI Risks Associated With NSAIDs and COX-2 Drive Patients To Use Other Classes of Drugs

ABT-594

Cost Through Go/No Go

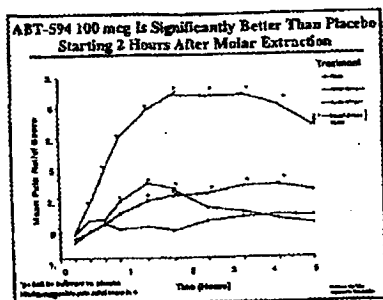
Neuropathic	\$ 15
MM	
OA and Neuropathic	\$ 20
MM	

Determining Sample Size and Power

	Well Powered Study	Under-Powered Study
Example	Pivotal Phase III Trials	Phase II, proof-of-principle
Driver	80% power to detect acceptable difference with $\alpha = 0.05$	Efficiency in answering fundamental efficacy and safety questions; threshold effect
Output drug	Definitive study Submit to FDA for approval	Demonstrate potential of
Paraphrases	Proof-of-principle studies Dose-ranging Knowledge of pharmacology	Practical data

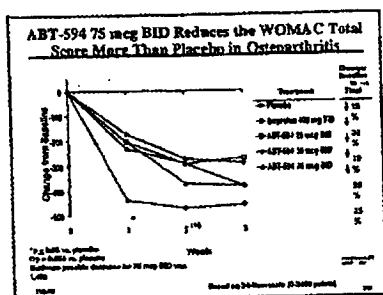
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ABBT 0019119



ABT-594 vs. Celebrex

Event	Celebrex 200 mg BID	Placebo	ABT-594 75 mcg BID	Placebo
Dyspepsia	8.8 %	(5.2 %)	4 %	(0 %)
Diarrhea	5.6 %	(5.6 %)	3 %	(7 %)



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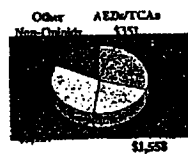
ABT 0019120

ABT-594 Project Review
November 17, 2000

Commercial Assessment

Andrea Landsberg
Laura Robinson

U.S. 1999 Pain Market Sales (\$MM)



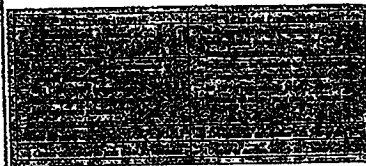
Total US Market \$7.8 Billion
ROW Market \$XXX

- Pain market is growing due mainly to Cns-2s, but also increased awareness of need to aggressively tx pain and increasing caution with opioid use
- Cns-2 sales will likely top \$4 billion in 2000
- PCPs as group are key pain prescribers
- Neuropathic pain prescriptions also include neuroleptics, orthopedic surgeons, palliative, pain specialists, oncologists

Pain Markets Considered for ABT 594

- Acute and chronic pain
- Chronic pain
 - nociceptive and neuropathic
- OA/RA
- Neuropathic pain
 - diabetic polyneuropathy pain
- Moderate to moderately severe pain

ABT 594: Current vs DDC Profile



Indication and Spillover Potential

- Market research conducted x/99?
- Make table with share% in various markets depending upon indication
- clarify product profile in study vs current knowledge

Neuropathic Pain Market



- Reduced growth rates over time to years very low XXX to YYY
- 3 values impacted by high use of generic: Pregabalin may significantly grow market sales
- MSAIDS, though not very effective, are also used as first line treatment for neuropathic pain (particularly by PCPs) and are not reflected in above market sales

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ABBT 0019121

Neuropathic Pain Competition

[illegible]

Unmet Needs in Neuropathic Pain

- More complete efficacy than that provided by Neurontin
 - including increase in responder rate
- Efficacy matching Neurontin, with reduced side effects
- Treatments with reduced or no titration
- Improved dosing schedules, ideally QD
- Formulation options for single compound
 - patch, parenteral, solution, sprinkle, melt

Neuropathic Pain Market Drivers

- Growth in underlying conditions such as diabetes, cancer, herpes
- Improved treatment/prevention of underlying conditions
- A win-win of effective and well-tolerated treatment leading to improved screening and diagnosis
- FDA approval for neuropathic pain to allow for professional and DTC promotional efforts

↑

Long term

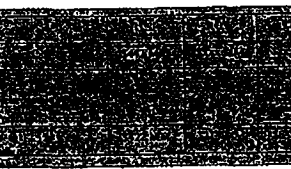
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Potential Positioning of ABT 594 in Neuropathic Pain

- **First line therapy:**
 - Improved efficacy over AEDs and TCAs with 'comparable' SEs
 - Novel therapy approved for neuropathic pain
- **Second line therapy**
 - Comparable efficacy and AEs as current therapies for non or partial responders

ABT 594 Forecast



14-00000

14-00000

ABT 594 Forecast Assumptions

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ABBT 0019122

Key Product Challenges

- Tolerability
 - Competition has clear advantage on tolerability
 - Potentially low therapeutic index
 - PCP market will be particularly impacted
- Nicotinic mechanism
 - Will require pre-launch market education and pricing to both diffuse negative associations and generate excitement (surrounding novel MOA)

backups

Commercial Assessment

Andrea Landsberg
Laura Robinson

Complexity of Segmenting the Pain Market

- Pain Market can be segmented in a variety of ways
 - Duration
 - Persistent, Acute, Chronic
 - Severity
 - Mild, Moderate, Severe
 - Pathophysiology
 - Neuropathic, Nociceptive, Mixed
 - Etiology
 - Cancer, Injury, Infection, Metabolic (DM), Immunologic (RA), etc.
- Each classification is relevant for almost every pain patient

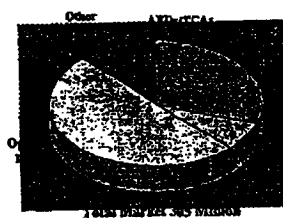
U.S. Pain Market Growth 1997 to 1999

	TRx CAGR 97-99	Sales CAGR 97-99
Other	5.3%	7.7%
Aspirin	5.3%	7.7%
NSAIDs	1.3%	1.9%
COX-2s	NA	NA
Opioids	2.5%	8.2%
Other Non-Pharm	1.0%	5.5%

Complexity of Segmenting the Pain Market

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 - Pathophysiology
 - Neuropathic, Nociceptive, Mixed
 - Etiology
 - Cancer, Injury, Infection, Metabolic (DM), Immunologic (RA), etc.
- Each classification is relevant for almost every pain patient

U.S. Pain Market TRx (MM)



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ABET 0019123

ABT-594 Project Review
November 17, 2000

Milestone Criteria

Bruce McCarthy
David Morris

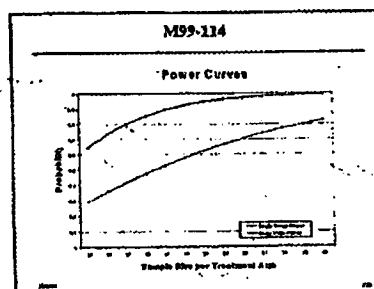
M99-114

Sample Size Rationale
N = 320 (80/group)
Type I error: 0.05
Power: 80%
Effect size: 0.46

Active Treatment
ABT-594 75mcg: 38% for NPS Total
Gabapentin: 39% diary
Placebo
ABT-594 75mcg: 10%
Gabapentin: 23%

M99-114

Sample Size Rationale
ABT-594 mean change from placebo = 11.4
standard error = 7.3
ABT-594 n = 18
Placebo n = 24
Gabapentin N=165 Completed = 82% (n = 135)
Gabapentin n = 82 mean change = 5.9
Placebo n = 80 mean change = 5.1

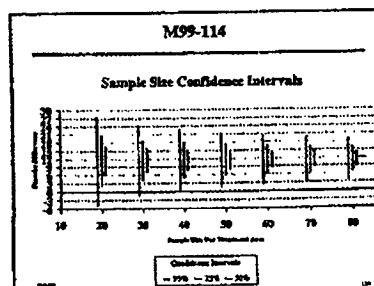


M99-114

Assumptions for Calculating Power of Three Comparisons

- Probability of single success is power of single comparison
- All doses are in efficacious range
- Comparisons are independent

Increases Type I error rate



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ABBT 0019124

ABT-594 Project Review
November 17, 2006

Toxicology

Reid Patterson

Oral Toxicology of ABT-594

Genotoxicity: Ames assay Mouse Lymphoma In vitro Cytogenetics Mouse Microsomes	Acute: Single dose in rat, dog, mouse
Multidose: rat: 2 wk, 1 mo, 3 mo, 6 mo, 2 yr monkey: ESR, 1 mo, 3 mo, 12 mo mouse: 2 wk, 3 mo, 2 yr	D.A.R.T.: Dose range (x2) Segment I Segment II (x2) Segment III

Metabolism Studies with ABT-594

- Metabolic fate in rat, monkey, mouse, humans
- In vitro metabolism in liver microsomes
- Metabolite identification
- Protein binding and site of binding
- Red cell binding
- Tissue distribution (pigmented and nonpigmented rat)
- p450 characterization and inhibition
- Melanin binding
- Placental/fetal transfer

Pharmacology Studies with ABT-594

- Effects on respiration
- Bronchoconstriction
- Cardiovascular/renal profile
- Drug discrimination
- Abuse potential - self administration

Azetidine Mesylate Residues in ABT-954

- All mutagenicity tests negative with ABT-594
- Back-up NCE ABT-259 was marginally positive in Ames Assay
 - Confined to TA-1535 strain & confirmed on replication
 - Highly purified lots were consistently negative
 - Impurity isolated and identified as BOC azetidine mesylate
 - 3.5 µg/plate threshold for positive Ames
 - 2.5 µg/plate (0.02% at % ABT-259) was negative

Azetidine Mesylate Residues in ABT-954

- Similarity in synthesis led to measurement in ABT-594
 - Lot Ames negative had 0.02% azetidine mesylate
 - Lot with 0.03% used in Phase I -
 - 600 µg/day x 14 days or 900 µg/day x 10 days
 - Lot with 0.02% used in Phase II - 900 µg/day x 6 wks
 - (36 µg/ml blood, 3 ng/g, 0.18 µg/day)

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ABT 0019125

Azetidine Mersylate Residues in ABT-594

- Despite negative Ames, sought to reduce LOQ
 - Achieved pQL of 0.005% or 50 ppm
 - Achieved pQL of 0.002% or 20 ppm
- Proved recrystallization was <pQL at lab and full scale
 - Phase III clinical lots demonstrate no residue
- Identified Mitsunobu method to replace AZ alkylation step
 - Transient alkylating agent, leaving no impurity
 - First lot 4/01 for clinical use

Carcinogenicity Assessments of ABT-594

- 07/01/98 Dose selection proposal prepared
- 08/31/98 Teleconference on proposal
- 09/22/98 FDA letter accepting rat dose at 25X AUC rejecting mouse doses, wasted more on cause of deaths in satellite and main study groups
- 10/02/98 Recommended higher top dosage (2 mg/kg)
- 11/20/98 Recommendation submitted to FDA
- 12/02/98 FDA accepted original dosages owing to deaths
- 04/30/99 Identified few rat hepatic basophilic foci (6 mo)
- 01/25/00 FDA accepted strategy for early termination of low-dose male group owing to low survival

Metabolic Data from ABT-584

- F₁₀₀= 80% (cyano), 78% (mouse), 61% (rat), 35% (dog)
- Emesis above 25 mg/kg in dog precluding use as model
- Fasting reduces emesis but has no effect on PK
- Widely distributed; brain 2X plasma
- Predominantly parent (47-79%) in circulation
- T_{1/2} rapid (<90 min) in all but monkeys (2.2 hr)

Metabolic Data from ABT-584

- Protein binding: 70% (human), 62% (rat), 45% (dog), 36% (mouse), 26% (cyto)
- Renal excretion of parent major route of clearance (70-992%)
- CL rate: mouse (4L/kg/hr) > rat > monkey > dog (0.4L/kg/hr)
- CYP2D6 plays minor role in metabolism
- Thirteen metabolites present in all species and humans
- N-glucuronide (M8) and ring-opened COOH (M1) major

Safety Margins in Animal Toxicity with ABT-594

Lowest Toxic Dosage (mg/kg) & AUC (ng·h/mL):		
Mouse: 3 mo.	3.0	413-735
Rat: 3 mo.	2.0	1281-1784
6 mo.	0.2	221-329
Monkey: 3 mo.	0.2	288-321

Highest Non-Toxic Dosage (mg/kg) & AUC (ng·h/mL):		
Mouse: 3 mo.	1.0	142-226
Rat: 3 mo.	0.3	319-433
6 mo.	<0.2	<221-329
Monkey: 3 mo.	0.1	75

Toxicity Observed with CCM ABT-594

Signs: pallor, prostration, hypothermia, convulsion, decreased activity, tremors, salivation, rapid breathing, lethargy, anorexia, partial alopecia, diarrhea, emesis, death

General Observations:

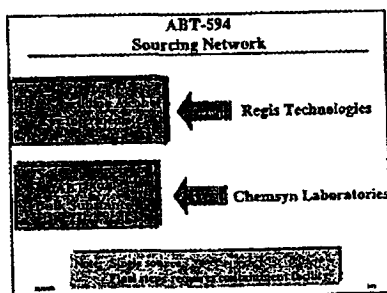
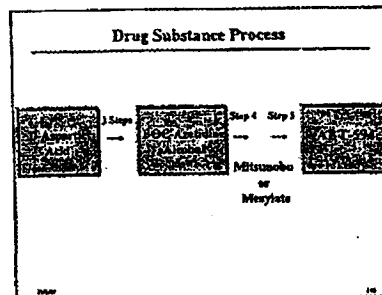
- Subclinical leucopenia (mice)
- Reduced growth (body weight, food consumption, etc)
- Elevated bile acids (rats)
- Hepatopathy: ↑ ALP, ALT & weight up, CHOL down, basophilic foci (rats)

DART Observations: postimplantation loss and abortions up, litter size and uterine weights down in maternally toxic rabbits

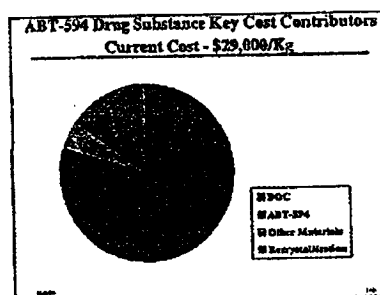
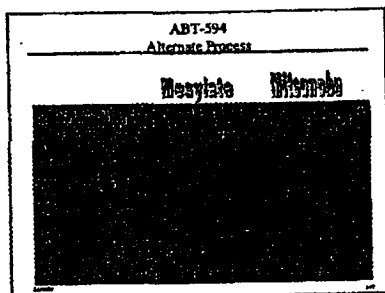
ABT-594 Project Review
November 17, 2000

Synthetic Route

Kathy McFarland



- ABT-594 Azetidine Mesylate Impurity**
- Impurity derived from Step 4 intermediate
 - Potential mutagenicity discovered with lot from ABT-259
 - Recrystallization reduces mesylate to <0.005%
 - Alternate Step 4 process eliminated mesylate (Mitsunobu)



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ABBT 0019127

New Potent Drug Facility
<ul style="list-style-type: none">• PPD / SPD / HPD/AI

Design Scope - Included
<ul style="list-style-type: none">• Chemical manufacturing<ul style="list-style-type: none">• 3 individual manufacturing cells• Reactors from 1500s to 3000s• Filter dryers / Multi-processing pots• Direct transition to Pharmaceutical manufacturing• Pharmaceutical manufacturing<ul style="list-style-type: none">• Soft elastic capsule unit• Solid dosage suite

Justification
<ul style="list-style-type: none">• 80% DCF ROI based on four compounds<ul style="list-style-type: none">- Rubitecan- ABT-627- ABT-594- Cis-Atracurium• 14 additional potent drugs in the pipeline

Capital
<ul style="list-style-type: none">• Bulk chemical manufacture: \$40MM• Pharmaceutical manufacture: \$20MM• Total: \$60MM• \$1MM in 2001 Plan for engineering design and planning approval

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ABBT 0019128

ABT-594 Project Review
November 17, 2000

Follow-On Strategy

Mike Meyer

Identification of ABT-594 Backup

Clinical results outline specific improvements required for backup

- Emesis
 - Modeled preclinically in ferret and dog
- Nausea
 - Ferret model can address nausea index
- Dizziness
 - Mouse rotarod
 - Rat Edge test

Discovery Program Basis

NNR Subtypes differentially mediate efficacy and side effects

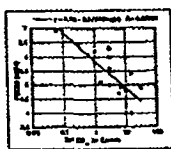
- Different NNR subtypes mediate analgesic effects of nicotinic agonists and adverse events
- Program committed to the identification of NNR subtype selective compounds
- Project initiated a 6-year collaboration with NeuroSearch
 - Access to human recombinant NNRs
 - Access to new structural classes of NNR modulators

Nociception Mediated by $\alpha 4$ Subtypes

- Mouse Knockouts support role of $\alpha 4$ and $\beta 2$
 - Key differences between pain type
- Role for $\alpha 4$ subtype in acute thermal pain (activation of descending inhibitory pathways)
 - Antinociceptive studies
 - Site injection studies
 - Antagonist studies
- Descending inhibition less important in persistent pain models, and even less so in neuropathic pain models

Emesis Mediated by $\alpha 3\beta 4$ Subtype

- In preclinical models, emesis is correlated to potency and efficacy at ganglionic ($\alpha 3\beta 4$) NNR subtypes
- Antagonist and route of administration studies suggest both local and systemic contribution



Is an Improved T.I. Feasible?

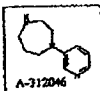
Highly selective $\alpha \beta 2$ NNR agonists can be identified and appear to be effective in acute pain models with a decreased side effect liability, but these compounds may not exhibit an ABT-594 like broad spectrum analgesic profile

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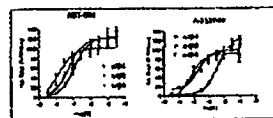
ABT 0019129

A-312046: Broad Spectrum Analgesic

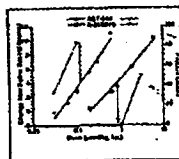
- Comparable efficacy to ABT-594 in models of acute, persistent and neuropathic pain
- Ten-fold lower potency vs. ABT-594
- Like ABT-594, retains efficacy upon repeated dosing in models of persistent and neuropathic pain

**A-312046: Moving Toward Selectivity**

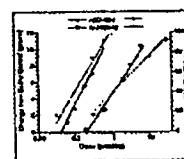
- A-312046 exhibits an improved NNR subtype selectivity profile relative to ABT-594
- A-312046 is highly selective for NNRs vs. other ion channel or GPCR targets

**A-312046: Decreased Emetic Liability**

- I.P. Administration:
 - Full efficacy in Chung model, 8-fold less potent than ABT-594
 - 70-Fold lower emetic liability

**A-312046: Oral Administration Studies**

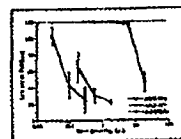
- Oral Administration:
 - Improvement in therapeutic index relative to emesis no longer evident
 - May be direct activation of afferent signalling from gut?

**A-312046: Mouse Models of TI**

- A-312046 exhibits significant improvements in several mouse models of toxicity

A-312046: Rat Model of Balance

- In Rat Edge Test model of balance, coordination, and muscle strength, A-312046 exhibits 200-fold improvement vs. ABT-594

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ABBT 0019130

**Therapeutic Index Comparison:
ABT-594 vs. A-312046**

Therapeutic index based on ratio of dose (i.p. administration) for adverse event and approx. ED₅₀ in Chung neuropathic pain model

	ABT-594	A-312046
Female	2.1	3.8
		4.3
Male	2.1	2.5
		2.2
Rat		2.4

A-312046: Pharmacokinetics and Metabolism

- Rat:
 - 80% Oral bioavailability, $t_{1/2}$ = 3 hr
 - 2:1 Partitioning into CNS
- Dog:
 - 13% Oral Bioavailability, $t_{1/2}$ = 2 hr
 - Radiolabeled studies demonstrate >90% absorption
- Monkey:
 - 3% Oral Bioavailability, $t_{1/2}$ = 1.5 hr

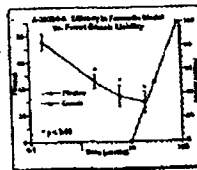
Apparent rapid first pass metabolism in dog and monkey

A-312046: Candidate for Transdermal Delivery?

- Potential to avoid direct emetic effects on the gut
- Avoid first pass metabolism
- Allow for better control of C_{max} (correlated to nausea and emesis for ABT-594)
- Commercially acceptable formulation for neuropathic pain
- Ongoing studies:
 - Transdermal delivery in monkey
 - Permeability in human cadaver skin

Subtype Selective NNR Agonists for Non-Neuropathic Pain

- A-333094:
 - Efficacy in acute and persistent pain models
 - Poor efficacy in neuropathic pain model
 - Enhanced α/β_2 subtype selectivity
 - Decreased emetic liability



ABT-594 Project Review
November 17, 2000

Intellectual Property

Steve Weinstock

Patent Coverage

Duration of Patent Coverage

- Compound
 - U.S. until 9 Sept. 2016
 - Foreign until 8 Oct. 2013
- Analgesic Indication
 - U.S. until 9 Dec. 2017
 - Foreign until 10 Dec. 2017

Patent Coverage

Extent of Foreign Patent Coverage

Compound

• Australia	• Japan
• Brazil	• Korea
• Canada	• Mexico
• Europe (Western)	• Philippines
• Israel	

Patent Coverage

Extent of Foreign Patent Coverage

Analgesic Indication

• Argentina	• Korea
• Australia	• Mexico
• Brazil	• Norway
• China	• New Zealand
• Canada	• Philippines
• Czech Rep.	• Poland
• Europe (Western)	• Slovak Rep.
• Hungary	• South Africa
• Israel	• Taiwan
• Japan	• Turkey

Patent Issues

- No third-party patent domination of:
 - compound
 - use for analgesia of compounds identified by chemical structure
- Not aware of third-party patent domination of use for analgesia of compounds identified by properties

Patent Issues (cont'd)

- Third-party patents on some combinations
 - U.S. patent 6,054,451 to Algos on combination with NMDA antagonists
- Some possibility of interference on broad generic claim with SIBIA Neuroscience U.S. application
 - Abbott in strong position - filed 2.5 years earlier - 7 Oct. '92 vs. 7 Apr. '95

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ABBT 0019132

Potential Interference

- SIBIA PCT Publication WO 96/31475
 - Based on U.S. application filed 7 April 1995
 - Abbott application filed 4 October 1993
 - Has broad formula encompassing ABT 594 (Pyridinyl Ether)
 - No disclosure of specific Pyridinyl Ethers
 - 4 U.S. patents to other aspects of broad formula issued
 - U.S. application still pending

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ABBT 0019133

Depakote Follow-On Project

Strategic need to defend Depakote Franchise (patent expiration 1/08)

Goal:

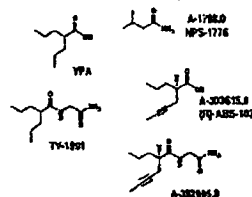
To identify a patent-protected compound that has similar or better efficacy to VPA in rodent models of epilepsy that may have the broad spectrum efficacy of VPA in epilepsy, bipolar disorder and migraine prophylaxis as a follow-on to Depakote.

NR: Mechanism of action of VPA in epilepsy, bipolar and migraine is unknown.

Tactics: In-house VPA analogs with demonstrated AE activity

Depakote Follow-On Project

VPA, TV-1801 and VPA Follow-On Compounds



Depakote Follow-On Project

DOC Strategy

Validate anticonvulsant pharmacology profile of R-ABS-103/NPS-1776 and A-302089.0 in direct comparison with VPA in mouse and rat models.

Toxic Test

Acute Toxicity (LD50)
Chronic Toxicity (NOAEL)
Developmental Toxicity (PND 12.5)
Altered Qualitative (Qualitative Performance)
Safety (Summary)

Preclude CF safety of R-ABS-103, NPS-1776 and A-302089.0 (Pilot).

Evaluate the PK, metabolism, toxicology and neurotoxicity of R-ABS-103 and A-302089.0 (Pilot).

Provide comparative data on VPA follow-on and recommend clinical strategy of DOC.

Depakote Follow-On Project

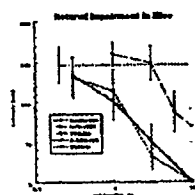
Activity Profile in Epilepsy Models

R-ABS-103, NPS-1776 and A-302089.0 have an efficacy profile similar to VPA in electroshock (MES) and pentylenetetrazol (PTZ) seizure models.

NPS-1776 and A-302089.0 have improved therapeutic indices relative to VPA.

Compound	ED50 (mg/kg)	ED50 (mg/kg) relative to VPA	ED50 (mg/kg) relative to VPA
VPA	1.0	1.0	1.0
NPS-1776	0.5	0.5	0.5
A-302089.0	0.5	0.5	0.5

Depakote Follow-On Project



Depakote Follow-On Project

VPA Follow-Ons

Compound	Therapeutic Index	Formulation	PK
VPA	1.2	Control vehicle	$t_{1/2} = 4-8$ h $t_{1/2} = 12$ h
NPS-1776	Equivalent to VPA	CR vehicle CR vehicle - 12.5 CR vehicle - 12.5	$t_{1/2} = 12$ h $t_{1/2} = 12$ h
R-ABS-103	Equivalent to VPA	CR vehicle - 12.5 CR vehicle - 12.5	$t_{1/2} = 12$ h $t_{1/2} = 12$ h
A-302089.0	Equivalent to VPA	CR vehicle - 12.5 CR vehicle - 12.5	Not tested

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Depakote Follow-On Project

VPA Follow-ons

	Drug Formulation	Coating Inhibition	Conformation	Toxicology
VPA	Black box	Yes	No identified issues	Black box
NPS-1776	No inhibition of polymer (p inhibition)	Yes	No	Toxicologic
R-ABS-103	No inhibition of polymer (p inhibition)	SP	SP	No pharmacology
A-352086	No inhibition of polymer (p inhibition)	SP	SP	Resolving additional compounds

All four compounds negative on genotoxicity

Depakote Follow-On Project

Formulation

VPA -

NPS-1776: Need controlled release formulation for clinical studies. Various formulations are under consideration that will provide 600 mg of compound in a controlled release preparation. Change: two large tablets (15 and 450 mg) twice a day. Does not require packaging change / NPS.

R-ABS-103: Proving difficult to make a solid dosage form of the drug. May need to consider a different capsule.

A-352086: A solid material. No work on specific formulations. Subject to synthetic compound intensity was based on experience with physical nature of R-ABS-103 and NPS-1776.

Depakote Follow-On Project

Compound Supply

NPS-1776: 400g on A-sheet for preclinical studies. NPS has 40g available.

R-ABS-103: 300g supplied by ABS. 200g due by 1/10. Delivery date delayed due to delay in signing contract.

A-352086: 25g synthesized. Additional compound available 11/17.

Depakote Follow-On Project

Toxicology

VPA: Toxicologic - black box warning

NPS-1776: Toxicologic in rats.

R-ABS-103: Does not cause neurotoxicity in mice at non-maternally toxic doses (ABS data). GLP toxicology study planned for December start.

A-352086: Additional supply of compound required for study. Synthesis complete 11/17.

Depakote Follow-On Project

Compound	Formulation	Coating	Conformation	Toxicology
VPA	Black box	Yes	No identified issues	Black box
NPS-1776	No inhibition of polymer (p inhibition)	Yes	No	Toxicologic
R-ABS-103	No inhibition of polymer (p inhibition)	SP	SP	No pharmacology
A-352086	No inhibition of polymer (p inhibition)	SP	SP	Resolving additional compounds

Depakote Follow-On Project

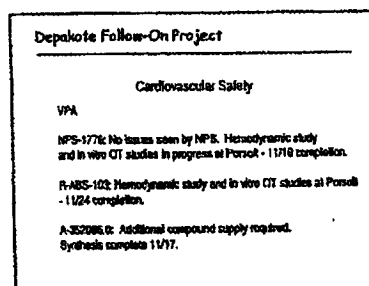
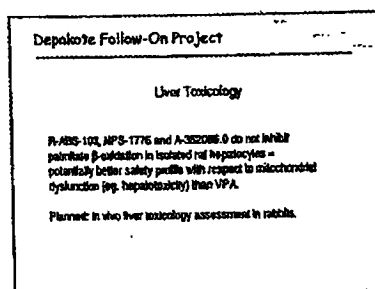
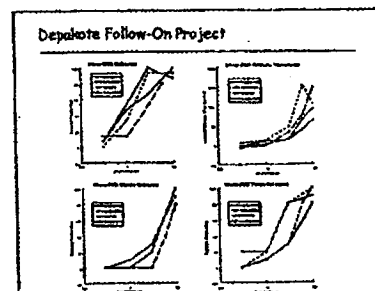
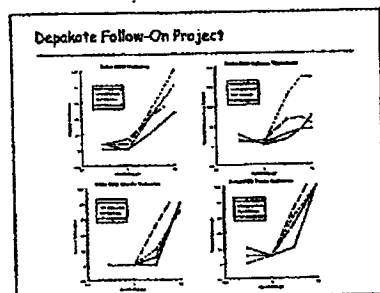
Genotoxicity

VPA

R-ABS-103, NPS-1776 and A-352086 are negative in mutagenicity and chromosomal aberration assays.

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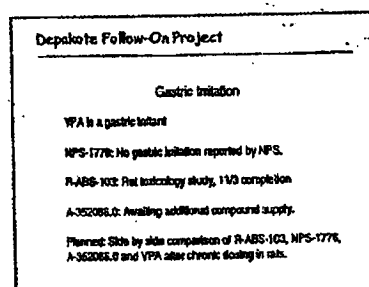
ABBT 0019135



Depakote Follow-On Project

Pharmacokinetics

Study ID	Study Type	Study Design	Study Population	Study Objectives	Study Results
NPS-1776	Phase I	Randomized, Double-Blind, Placebo-Controlled	Healthy Volunteers	Assess safety, tolerability, and PK of NPS-1776	Completed 11/18
R-ABS-102	Phase I	Randomized, Double-Blind, Placebo-Controlled	Healthy Volunteers	Assess safety, tolerability, and PK of R-ABS-102	Completed 11/24
A-352065.0	Phase I	Randomized, Double-Blind, Placebo-Controlled	Healthy Volunteers	Assess safety, tolerability, and PK of A-352065.0	Completed 11/17

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Depakote Follow-On Project

DDC Testing Issues

- Pharmacology package complete (in regards of how fast weight gain, bipolar or epilepsy efficacy)
- AB5-102 data not supported by Parallel data
- CV, PK, stability studies should be completed by 12/1/00
- Toxicology/behavioral studies incomplete - and going on phase
- A-352086 - testing other compounds due to compound supply
- NPS 1776 - 32 Mm too slow M2
- DDC decision based on physicochemical/bioassay/toxicology safety data
- Litico in-house - 1/1/00

Depakote Follow-On Project

Issues in evaluating VPA Follow-on Compounds

- Compound Supply
- Activity profile versus VPA in epilepsy models
- Use Toxicology
- Gastric Intestine
- Formulation
- Genotoxicology
- Cardiovascular Safety
- Toxicology

Depakote Follow-On Project

Pharmacokinetics

VPA

NPS-1776: Rapidly absorbed and eliminated after oral dosing in humans - $C_{max} = < 10\%$; $T_{1/2} < 3$ hrs. (NPS data)

R-AB5-102: PO in dog - $C_{max} = 1$ hr; $T_{1/2} < 1$ hr

A-352086: In progress, 10% < 5% R-AB5-100 in plasma after PO dosing in rats.

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McCarthy Deposition Exhibit 27

P's Exhibit DU

December 2000
ABT-594 Project Status Report

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture	Closing of enrollment on M99-114 as of January 5, 2001	<ul style="list-style-type: none"> Enrollment will be closed on this revised date. Timeline impact will be reviewed in January
PARD	During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study	<ul style="list-style-type: none"> This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made. Due to significant chemistry challenges, the delivery of impurity F' to PARD from SPD is delayed. New target date to be determined pending favorable results from current synthesis efforts. PARD Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot: planned January 2001 When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic	PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found.
NPD	Portfolio analysis process is underway for ABT 594 and will impact budget allocation for 2001. A new forecast using updated NPD forecast model with clearly defined product profile and high and low case estimates is being developed and will be reviewed by core team prior to final conduct of portfolio prioritization.	Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision.
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long-term toxicology studies.	ABT 594 portfolio team reviewed the forecasts and profile on 12/19/00. Final adjustments are in process, and will be completed no later than 1/15/01 (just prior to prioritization meeting).

2 of 6

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EXHIBIT
mclachry

27
9/23/01 m. ab

December 2000
ABT-594 Project Status Report

Project Cost Summary - November						
\$000's Activity	Cumulative through 1999	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	22.9	7.5	7.5	7.9	.4	157.1
CMC (PARD & SPD)	13.0	2.9	2.9	2.6	-.3	27.6
Drug Safety	8.7	3.4	3.4	2.4	-1.0	18.3
Other Support Costs	0.7	.5	.5	1.5	1.0	12.2
Total	50.5	14.3	14.3	14.4	.1	215.2

File NDA = 9/2003

Clinical Study Progress					
Protocol # - Study Name	Start (1st Patient Dosed)	End (Last CRF in House)	Total R/OSS \$000	Total Target Patients	Current Enrollment
M99-114 - A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,000	320	267 (As of 12/31)

3 of 6

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December 2000 ABT-594 Project Status Report

Business Rationale

Date: November 2000
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594
Trade & Generic Name: TBD, ebanciline losylate
Mechanism of Action: Neuronal Nicotinic Receptor (NMR) Agonist

Indications: Neuropathic Pain
Chronic Pain (publication only)

Product Profile

Attribute	Date Defined	Probability	Confirm Status	Share Impact
Not scheduled	12/1996	High	1004	High
Chronic nociceptive pain efficacy	10/1999	Medium	2001	High
Neuropathic pain claim	6/1999	Medium	2001	High
General pain claim	12/1996	N/A	N/A	High
Moderate to moderately severe pain				
No tolerance/dependence or withdrawal	9/1998	Medium	1003	High
Very few abnormal LFTs	9/1998	High	2001	High
Low nausea/vomiting at effective dose	6/1999	Medium	2001	High
Other safety OK	9/1998	Medium	2001/1003	High
No differential efficacy (nicotine users vs. non users)	9/1998	High	2001/1003	High
No differential side effect profile (nicotine users vs. non users)	9/1998	Medium	2001/1003	Medium
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	Low	4001	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium
8/10 dosing	6/1999	High	2001	High
No major drug interactions	12/1996	High	1003	Medium
Titration of 2.5 days duration is required to minimize nausea and vomiting at effective dose.	9/1999	Medium	1000	High

* Probability Key:

High = 70-100%
Medium = 30-69%
Low = 0-29%

Market Forecast

Patent Status:	PPC/IDC 12/1996*	Plan as of 6/1998*	Current Revised 1/2001**
NDA Filing:	10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
Ex-U.S. Filings:	12/1999 (acute) 6/2001 (chronic) Same as above - Eur N/A - Jpn	12/2001 12/2001 - Eur 12/2003 - Jpn 6/2003	9/2003 9/2003 9/2003 9/2004
Projected U.S. Launch:	12/2001 (acute) 12/2002 (chronic)		
Projected ex-U.S. Launches:	Same as above - Eur N/A - Jpn	12/2003 - Eur 9/202004 - Jpn	Q2 2005 'Average' launch for EU, LA, Canada) Q4 2005 (Average launch for Japan, PAA) 20% (Neuropathic pain) 5% (Persistent Chronic Pain) same as US assumptions \$339
Peak TRx Share, U.S.:	6.6% (patients)	5% (Rx)	
Peak TRx Share, ex-U.S.:	5.4% (patients)	5% (patients)	
Peak Sales, U.S. (\$MM)	\$285	\$618	
Peak Sales, ex-U.S. (\$MM)	\$308	\$310	\$466
Pre-Tax NPV @ 12.5%, ex-U.S. (\$MM)	\$338	\$305	\$535
After-Tax NPV @ 12.5%, U.S. (\$MM)	\$412	\$813	\$316
Avg. daily dose	50 mg	200 mcg	150 mcg
Target Drug Cost/kg at Launch	\$2,500	\$2,500	\$40,000 (base eq.)
SMM at Launch (US)	94.8%	97.2%	91.6%
SMM at Year 5 (US)			92.2%

* Forecast based on general pain target indication

** Forecast based on neuropathic pain indication and published study in chronic pain

4 of 6

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December 2000
ABT-594 Project Status Report

Project Overview

Metrics Dates

Description	Date
ODC Meeting	12/1995 (PBOC)
Start of first GLP animal tox study	2/1997
First dose in human (beg. Phase I)	7/1997
First dose in patient (beg. Phase II)	7/1998
First Onset in Phase III	2/2002 (est.)
Last Patient/Last Visit	4/2003 (est.)
NDA Filing	9/2003 (est.)
NDA Approval	9/2004 (est.)
Europe (EMEA) Filing	9/2003 (est.)
Europe (EMEA) Approval	TBD
Japan Filing	4/2004 (est.)
Japan Approval	TBD

PARD

Activity	Plan 6/1999	Current Revised 10/00	Actual
Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
Phase IIb / Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lots (3) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 6/1999	Actual Date	Plan 6/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.8 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	On Test	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	On Test	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (7osylate Salt)

Toxicology

Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	-	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

5 of 6

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December 2000
ABT-594 Project Status Report

Clinical Study Progress

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Target Cost: \$3 MM

Actual Cost: TBD

Status: Ongoing – 267 patients randomized as of 12/31

Major Findings: TBD

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6 of 6

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McCarthy Deposition Exhibit 29

D's Exhibit 584



Marilyn J
Collicott /LAKE/PPRD/ABBO
TT
12/14/2000 12:20 PM

To JSCHANZENBACH@rsi-nc.com@internet
cc
bcc
Subject Study Termination

Hi John

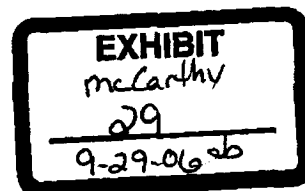
We've decided to end enrollment as of 1/5/01. The attached letter (which explains our reasoning) will be fedexed out to all investigators today. You may get some phone calls tomorrow. Let me know if you have any questions. Thanks.....mc



stopenroll

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ABBT233539



December 14, 2000

<name>
<address>

RE: Protocol M99-114: A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Neuropathy

Dear Dr. <name>,

We have decided to end enrollment in the above referenced study on January 5, 2001.

As specified in the protocol, 80% power would have been achieved with the randomization of 320 subjects, assuming there were no premature terminations. Our current premature termination rate, however, will result in less than 80% power even if we were to reach our enrollment goal. After reviewing possible outcomes with our statisticians, we concluded that ending enrollment prior to reaching our goal of 320 subjects will not meaningfully change our ability to interpret the results of this study. In addition, the sooner we review the data from M99-114, the sooner we may be able to move forward into Phase III.

In order to allow you to enroll any subjects that may have already been scheduled, the last date for randomization into study M99-114 will be 1/5/01. We sincerely apologize if this causes you or your staff any inconvenience.

The Analgesia Venture thanks you for your hard work and dedication to ABT-594 and study M99-114. Your efforts have allowed us to move forward more quickly than anticipated. If you have any questions or concerns please don't hesitate to contact me.

Sincerely,

Marilyn Collicott
Clinical Project Manager
Analgesia Venture

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ABBT233540

McCarthy Deposition Exhibit 30

P's Exhibit ED

January 2001
ABT-594 Project Status Report

Monthly Highlights

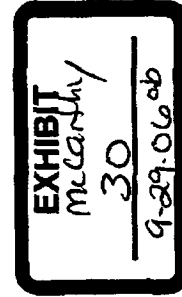
- Enrollment closed for our Phase IIB Painful Diabetic Polyneuropathy trial (M99-114), with total enrollment reaching 269. The last patient will complete the study at the end of February, and results will be available at the end of May.

Key Progress Gauges - January Accomplishments

Key Progress Gauges - January Accomplishments	Target Date	Status
• Close enrollment into M99-114	01/05	Complete
• Portfolio analysis team analyses submitted to Chris Turner	01/15	Complete
• Prepare study close-out timelines	01/22	Complete
• Complete preparations for February 2 Project Review with Jeff Leiden and Senior Management	01/31	Complete

February Projections

February Projections	Target Date	Status
• Project Review with Jeff Leiden and Senior Management	02/02	
• 250 completed Case Books in-house for M99-114	02/28	



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1 of 6

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January 2001
ABT-594 Project Status Report

Key Issues/Decisions/Events

Area	Issue/Decision/Event	Progress
Venture	Closed enrollment on M99-114 on January 5, 2001	<ul style="list-style-type: none"> Complete
PARD	During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F') was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F' and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study	<ul style="list-style-type: none"> This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F' impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made. Due to significant chemistry challenges, the delivery of impurity F' to PARD from SPD is delayed. New target date to be determined pending favorable results from current synthesis efforts. PARD Analytical will be testing the F' material to confirm identity and match to impurity found in drug substance lot. When testing is successfully completed, F' material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics
SPD	Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.	PARD Analytical is completing analysis of lab-scale batch and intermediates to assure there are no new impurities to be found.
NPD	Portfolio analysis to be reviewed by Senior Management on January 29. Project review presentation to Jeff Leiden scheduled for February 2.	Plans are to manufacture a single production-scale lot in early-2001 with available raw materials, and to wait on the second and third NDA lots until after the Go / No Go decision. Portfolio analysis process is complete and forecasts have been updated. Base case forecast now reflects value of neuropathic pain indication only (publication in chronic nociceptive pain is considered upside, and a separate funding issue). Commercial presentation to Jeff Leiden complete.
Toxicology	6-month rat study finding may suggest future possible occurrence of hepatocellular neoplasms in long-term toxicology studies.	No adenomas have been found in the study. The in-life phase of the 2-year carcinogenicity study is complete and preliminary data on tumor findings should be available 1Q2001.

2 of 6

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January 2001
ABT-594 Project Status Report

Project Cost Summary – November

\$000's Activity	Cumulative through 2000	YTD Actual	Projected Year-end	Current Funded Year-end	Variance	Cumulative to NDA
Clinical Program	34.8	0.8	6.2	6.2	...	150.9
CMC (PARC & SPD)	16.3	0.2	1.0	1.0	...	26.6
Drug Safety	11.6	0.1	1.4	1.4	...	16.9
Other Support Costs	2.1	...	0.7	0.7	...	11.5
Total	64.8	1.1	9.3	9.3	...	205.9

File NDA = 9/2003

Clinical Study Progress

Protocol # - Study Name	Start (1 st Patient Dosed)	End (Last CRF In House)	Total R/OSS \$000	Total Target Patients	Current Enrollment
M99-114 – A Randomized, Double-Blind, Placebo- Controlled Comparison of the Safety and Efficacy of ABT- 594 to Placebo in Subjects with Painful Diabetic Polyneuropathy	04/00	04/01	3,100	320	269 (Final)

3 of 6

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January 2001 ABT-594 Project Status Report

Business Rationale

Date: January 2001
Franchise: Neuroscience
Venture: Analgesia

ABT #: ABT-594

Trade & Generic Name: TBD, ebanciline tosylate

Mechanism of Action: Neuronal Nicotinic Receptor (NNR) Agonist

Indications: Neuropathic Pain

Product Profile

Attribute	Date Defined	Probability*	Confirm Status	Share Impact
Not scheduled	12/1998	High	100%	High
Chronic nociceptive pain efficacy	10/1999	N/A	N/A	High
Neuropathic pain claim	6/1999	Medium	2001	High
General pain claim	12/1998	N/A	N/A	High
Moderate to moderately severe pain				
No tolerance/dependence or withdrawal	9/1998	Medium	100%	High
Very low abnormal LFTs	9/1998	High	2001	High
Low nausea/vomiting at effective dose	6/1999	Medium	2001	High
Other safety OK	9/1998	Medium	2001/1003	High
No differential efficacy (nicotine users vs. non users)	9/1998	High	2001/1003	High
No differential side effect profile (nicotine users vs. non users)				
No reinitiation of cravings in ex-nicotine users	9/1998	N/A	N/A	Medium
Onset of action comparable to other therapies for chronic nociceptive pain	6/1999	N/A	N/A	Medium
Onset of action comparable to other therapies for neuropathic pain	6/1999	N/A	N/A	Medium
8/10 dosing	6/1999	High	2001	High
No major drug interactions	12/1998	High	100%	Medium
Titration of 2-5 days duration is required to minimize nausea and vomiting at effective dose	9/1999	Medium	100%	High

Market Forecast

PPCCDDC 12/1998*	Plan as of 6/1998*	Current Revised 1/2001**
10/2010 (est.)	10/2016 (est.)	10/2016 (est.)
12/1998 (acute)	12/2001	9/2003
6/2001 (chronic)		
Same as above - Eur	12/2001 - Eur	9/2003
N/A - Jpn	12/2003 - Jpn	9/2004
12/2001 (acute)	6/2003	
12/2002 (chronic)		
Same as above - Eur	12/2003 - Eur	Q2 2005 ("average" launch for EU, LA, Canada)
N/A - Jpn	9/20/2004 - Jpn	Q4 2005 (Average launch for Japan, PAA)
6.6% (patients)	5% (Rx)	20% (Neuropathic pain)
		5% (Persistent Chronic Pain)
5.4% (patients)	5% (patients)	same as US assumptions
\$285	\$618	\$339
Peak Trx Share, ex-U.S. (\$MM)		\$353
Peak Sales, ex-U.S. (\$MM)	\$308	\$353
Pre-Tax NPV @ 12.5%, ex-U.S. (\$MM)	\$338	\$356
After-Tax NPV @ 12.5%, U.S. (\$MM)	\$412	\$313
Avg daily dose	50 mg	150 mcg
Target Drug Cost/kg at Launch	\$2,500	\$40,000 (base eq.)
SMM at Launch (US)	84.8%	91.6%
SMM at Year 5 (US)		92.2%

* Forecast based on general pain target indication

** Forecast based on neuropathic pain indication (diabetic polyneuropathy)

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4 of 6

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January 2001
ABT-594 Project Status Report

Project Overview

Description	Metrics Dates	
	Date	
DOC Meeting	12/1996 (PPCC)	
Start of first GLP animal tox study	2/1997	
First dose in human (beg. Phase I)	7/1997	
First dose in patient (beg. Phase II)	7/1998	
First dose in Phase III	2/2002 (est.)	
Last Patient Last Visit	4/2003 (est.)	
NDA Filing	9/2003 (est.)	
NDA Approval	9/2004 (est.)	
Europe (EMEA) Filing	9/2003 (est.)	
Europe (EMEA) Approval	TBD	
Japan Filing	4/2004 (est.)	
Japan Approval	TBD	

PARD

Activity	Plan 8/1999	Current Revised 10/00	Actual
Phase I Formulation (PIB)*	7/1997	7/1997	7/1997
Clinical Supplies (PIB) for Molar Extraction	7/1998	7/1998	7/1998
Phase II Formulation (SEC) for IND	7/1998	7/1998	7/1998
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	10/1998	10/1998	10/1998
Phase III Formulation (HGC) for Bio Study	3/1999	3/1999	3/1999
Phase III Clinical Supplies Manufactured	9/1999	9/2001	TBD
NDA Lots (3) Completed	6/2000	5/2002	TBD
Completion of 1 Year Stability for NDA	7/2001	7/2003	TBD
Formulation Peer Review	10/2001	TBD	TBD

* Performed by IDC

SPD

Drug Substance Source/Lot #	KG	Plan 8/1999	Actual Date Received	Plan 8/1999 Projected Cost/kg*
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000
Chemsyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700
Chemsyn Mfg. Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700
Chemsyn NDA Lot #1	4.85 KG	10/1999	2/2001 **	\$ 29,700
Chemsyn NDA Lot #2	4.80 KG	10/1999	2/2001 **	\$ 29,700
Chemsyn NDA Lot #3	5.45 KG	10/1999	2/2001 **	\$ 29,700

* Target cost of drug substance at launch is \$20,000/kg (Toxylate Salt)

** Bulk manufactured 1/2001, but delivery delayed due to Mesylate testing & QA release

Toxicology

Toxicology Activity	Plan Start 1999	Actual Start Date	Report Completed
Gene Toxicology	2/1997	9/1996	8/1997
Acute Studies	3/1997	4/1997	8/1997
1 Month Rat/Monkey	2/1997	2/1997	11/1997
3 Month Rat/Monkey	7/1997	6/1997	8/1998
3 Month Mouse MTD	10/1997	6/1997	10/1998
SEG I and SEG II	10/1997	7/1997	7/1998
SEG III Rat (post natal development)	--	1/1999	Ongoing
6 Month Rat	1/1998	3/1998	7/1999
1 Year Monkey	6/1998	6/1998	3/2000
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing

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January 2001
ABT-594 Project Status Report

Clinical Study Progress

Protocol:

M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective:

The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses:

150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses:

Placebo

Target Enrollment:

320

Target Cost:

\$3 MM

Actual Cost:

TBD

Status:

Enrollment Complete – 259 patients randomized

Major Findings:

TBD

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6 of 6

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McCarthy Deposition Exhibit 37

P's Exhibit EL

Part 1

Project Review

ABT-089 and ABT-594

February 2, 2001

EXHIBIT
McCarthy
37
9-29-06 ab

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ABBT 0002314

Project Review

- ABT-089

REDACTED

- ABT-594

- Overview, upcoming milestone: June 2001
- Follow-on strategy

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ABBT 0002315

Neuronal Nicotinic Receptor (NNR) Program

- Scientific leadership position for Abbott
- An emerging diversity of receptors
- Multiple potential therapeutic targets

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ABT-089

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ABT-089

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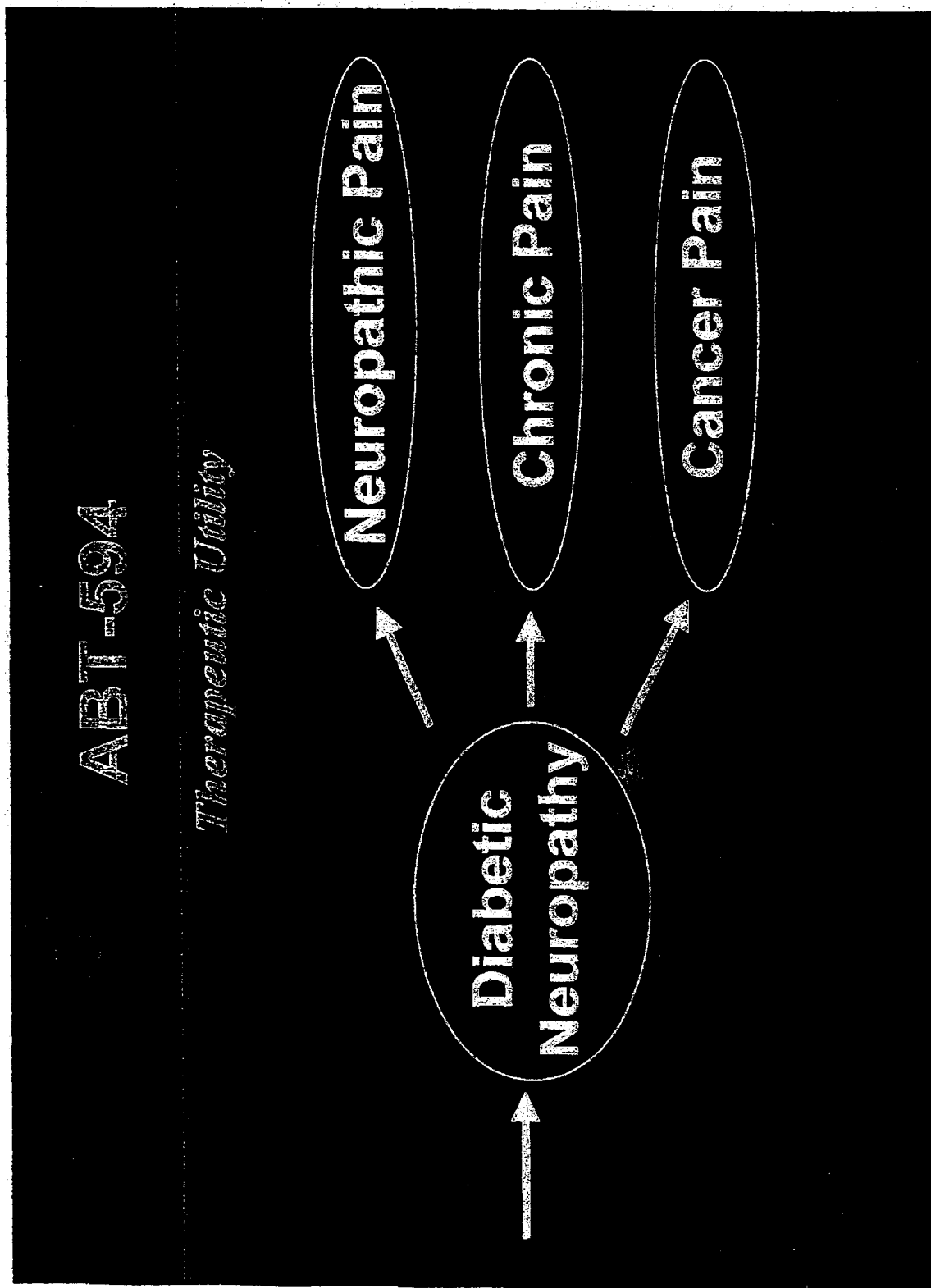
ABT-594

Overview

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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**ABT-594 Project Review
February 2, 2001**

Introduction

Chris Silber

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ABBT 0002359

ABT-594 Project Review

Agenda

- | | |
|---------------------------|------------------|
| ◦ Introduction | Chris Silber |
| ◦ Pharmacological Profile | Jim Sullivan |
| ◦ Clinical Overview | Bruce McCarthy |
| ◦ Commercial Assessment | Andrea Landsberg |
| ◦ Go/No Go Process | Bruce McCarthy |
| ◦ Follow-On Strategy | Mike Meyer |

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ABT-594

Overview

- First-in-class
- Analgesic potential demonstrated at 75 mcg BID
- Dizziness (7%), nausea (15%), vomiting (5%) observed at 75 mcg BID
- Full efficacy not determined
- MTD is 300 mcg BID
- Phase IIb in painful diabetic neuropathy, using doses up to 300 mcg BID ongoing
- Global sales: \$700 MM

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ABBT 0002361

McCarthy Deposition Exhibit 37

P's Exhibit EL

Part 2

Pain Prevalence

- 22% primary care patients worldwide have persistent pain
- Neuropathic pain
 - 20% of diabetics
 - 40% of HIV infected
 - 36% of cancer patients

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Pain Therapeutics Market

- \$12 billion in sales of key classes (NSAIDs, COX-2s, opioids, non-opioids)
- \$700 million in sales of key neuropathic pain compounds
 - use largely off-label
 - low cost generics

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Neuropathic Pain

Treatment

Some efficacy

(at best 40% vs. 20% placebo)

- Tricyclic antidepressants
 - Amitriptyline, desipramine, etc.
- Anti-epileptic drugs
 - Carbamazepine
 - Gabapentin (Pregabalin)
 - Topiramate, others
- Sodium channel blockers
 - Lidocaine
- Opioids
 - Tramadol

No efficacy

- SSRIs
- NSAIDs/COX-2

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**Broad-Spectrum, Non-Opioid Analgesic Activity
by Selective Modulation of Neuronal Nicotinic
Acetylcholine Receptors**

A.W. Bannon, M. W. Decker, M. W. Holladay, P. Curzon,
D. Donnelly-Roberts, P. S. Puttfarcken, R. S. Bitner, A. Diaz,
A. H. Dickenson, R. D. Porsolt, M. Williams, S. P. Arneric

SCIENCE • VOL. 279 • 2 JANUARY 1998

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ABBT 0002386

Development Strategy

Acute

Post-dental surgery
Sprains and strains
Acute back pain
Trauma
Post-general surgery
Post-orthopedic surgery
Dysmenorrhea
Renal colic
Biliary colic
Pancreatitis
Infections

Chronic Nociceptive

Osteoarthritis
Chronic back pain
Rheumatoid arthritis
Cancer pain
Fibromyalgia
Sickle cell disease
TMJ disorder
Bursitis
Tendinitis
Chronic visceral pain

Neuropathic

Diabetic polyneuropathy
Idiopathic polyneuropathy
Alcoholic polyneuropathy
Drug-induced polyneuropathy
HIV predominantly sensory neuropathy
Back pain
Cancer pain
Trigeminal neuralgia
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
Complex regional pain syndromes (I, II)
Atypical facial pain
Phantom limb pain

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Development Strategy

Choose Portals of Entry

Molar

Extraction

Acute Pain



**Peripheral
Neuropathy**

Neuropathic Pain



Osteoarthritis

**Chronic Nociceptive
Pain**



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ABST 0002367

ABT-594

Current Label Target

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

Upside Claim

- Neuropathic Pain
- Post herpetic neuralgia
- OA Pain
- Chronic Pain
- Cancer Pain

General Pain Claim

- Not viable due to 1.5 hour onset

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ABT-594

Go/No Go Process

- Decision analysis (DSG) will be used as a tool to determine milestone criteria
 - Efficacy and safety
 - Titration effects
 - Dose selection
 - Indications
 - Market research

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ABBT 0002369

ABT-594

Phase III Clinical Plan

	U.S.	Europe	Japan
Diabetic neuropathy	2 (n=1200)	2 (n=1200)	1 (n=300)
Long-term safety	1 (n=500)	1 (n=500)	-
Gabapentin comparator	-	1 (n=320)	-
Other neuropathic pain (Phase 3B) post herpetic neuralgia, sciatica	2 (n=600)	-	-
Cost (\$ million)	01 6.1	02 59.6	03 55.7
	<u>01</u>	<u>02</u>	<u>03</u>
	Total	121.4	

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ABT-594

Phase 2 to 3 Transition

Milestone review	6/01
End of Phase 2 package/request	9/01
Start manufacture Phase 3 supplies	9/01
Ship first Phase 3 supplies	2/02
Initiate Phase 3	3/02
Regulatory filings	9/03

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ABT-594

Overview

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- Global sales: \$700 MM

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**ABT-594 Project Review
February 2, 2001**

Pharmacological Profile

Jim Sullivan

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ABIT 0002373

ABT-594: Preclinical Pharmacology

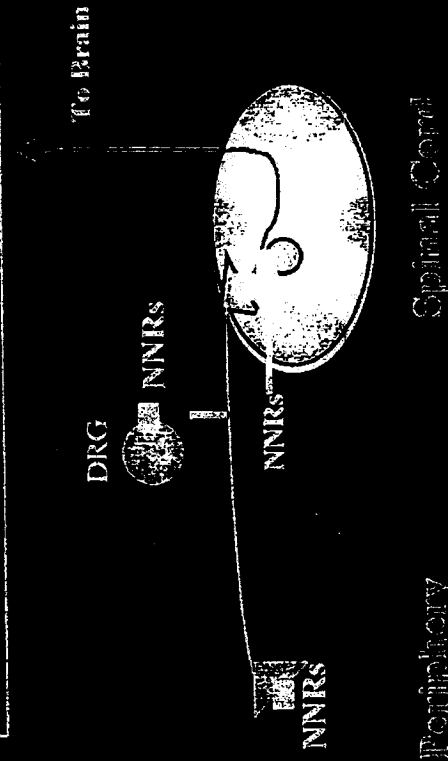
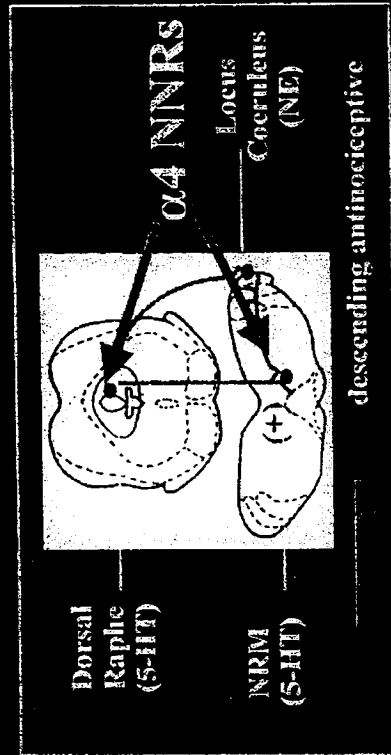
- Rationale for NNRS and pain
 - Knockout, antisense and pharmacological validation
- *in vitro* and *in vivo* profile of ABT-594
 - Efficacy
 - Safety

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ABBT 0002374

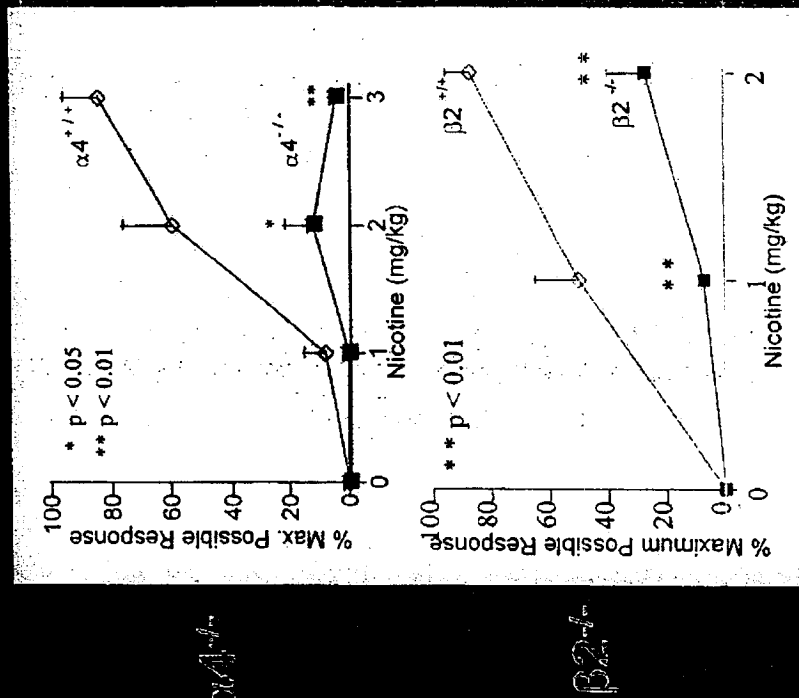
NNRs and Pain: NNRs are Expressed in Pain Pathways

- CNS
 - $\alpha 4$ NNRs are localized in NRM and dorsal raphe (Key CNS pain center)
- Spinal Cord
 - NNRs are expressed in dorsal horn neurons (key spinal cord pain processing center)
- Sensory Neurons
 - $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 7$ NNRs are expressed in DRG and on central and peripheral C-fiber nociceptors



NNRs for Pain: Role of $\alpha 4$ and $\beta 2$ NNRs Established Using Knockout Mice

In either $\alpha 4^{-/-}$ or $\beta 2^{-/-}$ mice, neither nicotine nor epibatidine was active in the hot plate assay (supraspinal mechanism)



Marubio, et al. *Nature* 1999 398, 805-810.

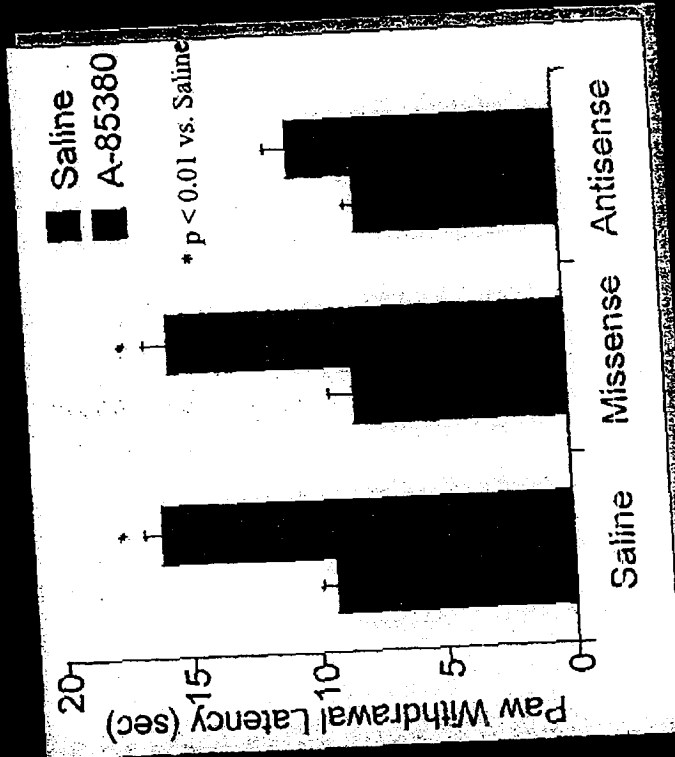
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ABB# 0002376

NNRS for Pain: Target Validation Using $\alpha 4$ Antisense *$\alpha 4$ Antisense Treatment Attenuates Antinociception in the Hot Box Model of Acute Thermal Pain*

Rats received either a saline, missense, or antisense continuous i.c.v. infusion (0.75 nmol/hr) for 7 days

Rats were evaluated in a crossover design in the hot box model of acute thermal pain



Bither, et. al, *Brain Res.* 871: 66, 2000

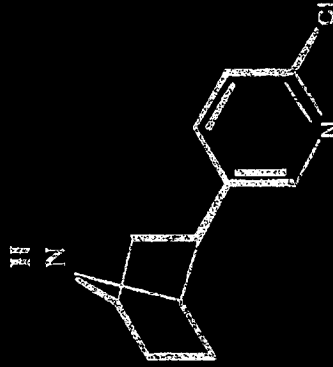
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Target Validation: NNR Agonists Are Analgesic



- NNR agonists are
 - Antinociceptive (capable of raising nociceptive thresholds in naïve animals)
 - Antihyperalgesic (capable of reversing the reduction in nociceptive thresholds following injury)
- Epibatidine (key discovery)
 - 200x more potent than morphine
 - Non-opioid
 - Potent NNR agonist
 - BUT highly toxic



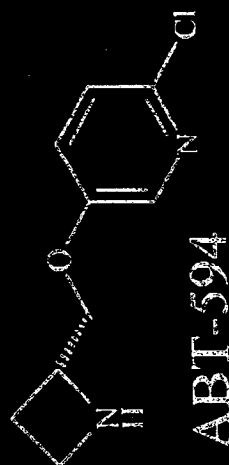
Radio and Dely, *Mol. Pharmacol.*
45: 563, 1994.

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NNRs and Pain: ABT-594

Goal



ABT-594

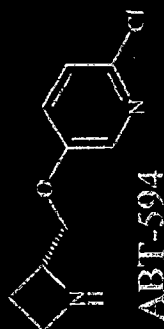
- Maintain broad spectrum analgesic efficacy of epibatidine
 - Maintain potency at $\alpha 4$ containing NNRs
- Decrease side-effect liabilities by decreasing activity at
 - Neuromuscular junction nicotinic receptors ($\alpha 1 \beta \delta \gamma$)
 - Ganglionic NNR subtypes ($\alpha 3 \beta 4$, $\alpha 3 \alpha 5 \beta 2 \beta 4$)

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ABT-594 is a More Selective NNR than Epibatidine in Radioligand Binding Studies

Binding Site (K _i ; nM)	Epibatidine	ABT-594
Cytisine Binding Site ($\alpha 4\beta 2$)	0.042	0.037
BTX Binding Site (Peripheral) ($\alpha 1$)	2.4	16,600



- ABT-594 retains potency of epibatidine at the $\alpha 4\beta 2$ binding site
- ABT-594 is > 5000-fold less potent than epibatidine at the peripheral neuromuscular junction nicotinic receptor

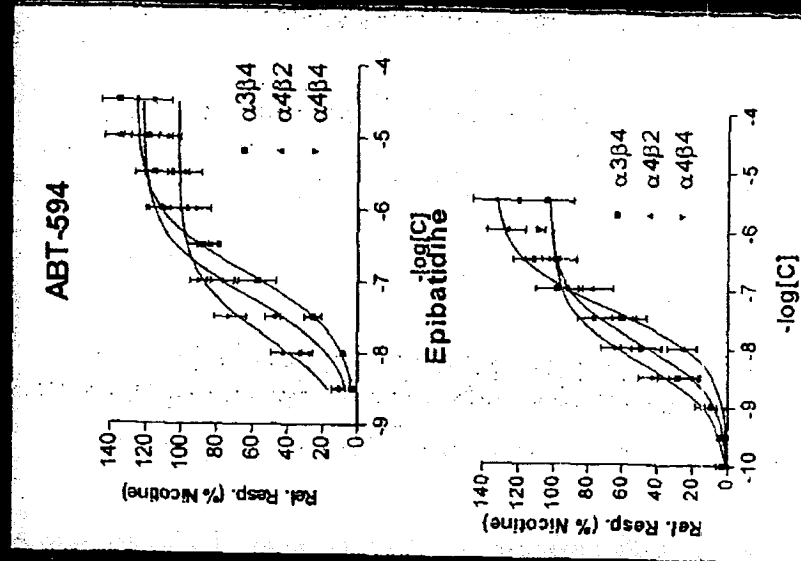
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ABB 0002380

In Vitro Functional Profiles of ABT-594 and Epibatidine

Functional Activity

- Rank order of potency
 - ABT-594: $\alpha 4\beta 4 \sim \alpha 4\beta 2 > \alpha 3\beta 4$
 - Epibatidine: $\alpha 4\beta 4 \sim \alpha 3\beta 4 \sim \alpha 4\beta 2$
- ABT-594 displays modest $\alpha 4$ vs $\alpha 3\beta 4$ selectivity
 - Compounds with greatly improved selectivity have been identified

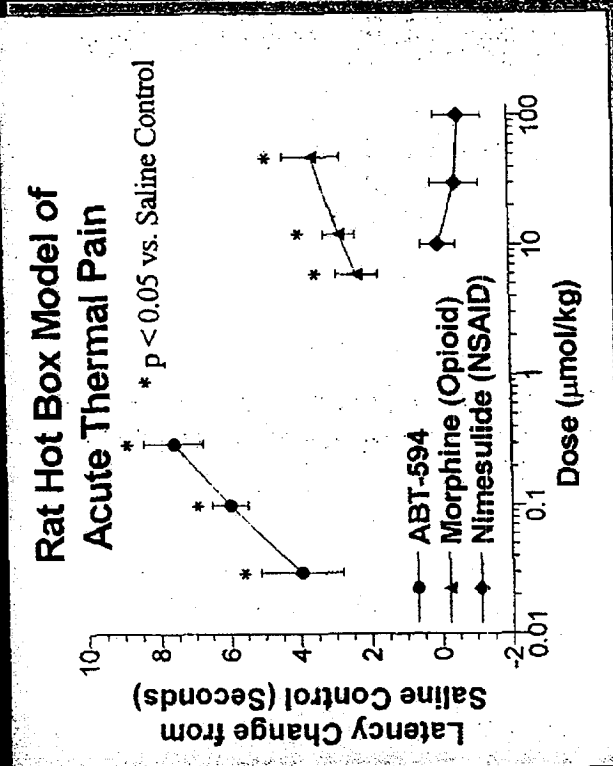


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ABT-594: In Vivo Efficacy in Models of Acute Thermal Pain

- ABT-594 is potent and efficacious in the Hargreaves Hot Box model of thermal nociception
- Onset of Efficacy = < 30 min
- Duration of efficacy ~ 2 hrs
- The effects of ABT-594 are blocked by the nicotinic antagonist mecamylamine, but not by the opioid antagonist naloxone



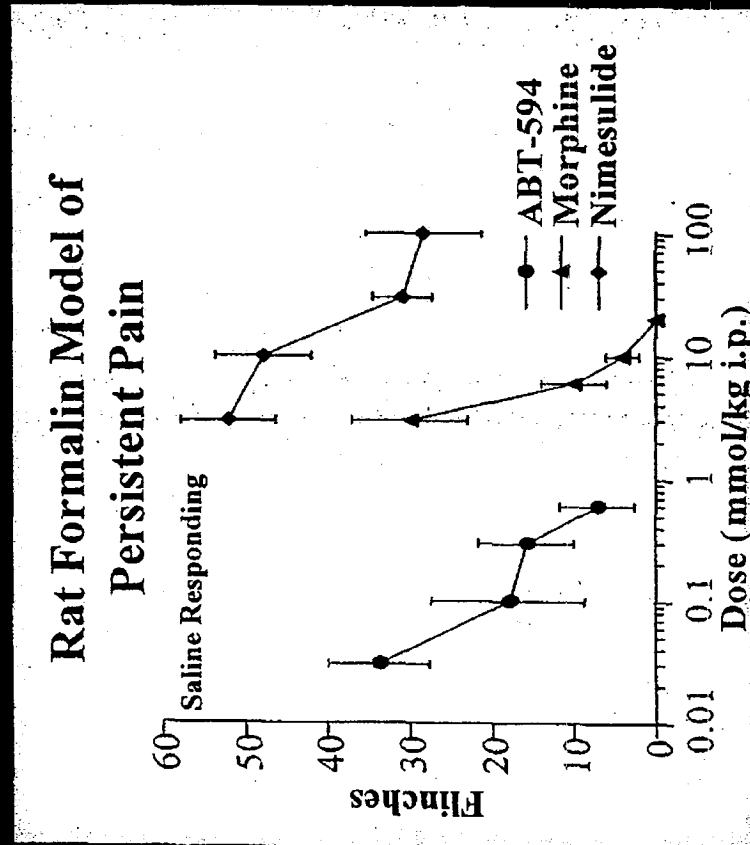
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ABBT 0002382

ABT-594: In Vivo Efficacy in Models of Persistent Pain

ABT-594 exhibits comparable efficacy and 50-fold greater potency than morphine in Phase II of the formalin model of persistent chemical pain

ABT-594 is active upon both i.p. and oral administration

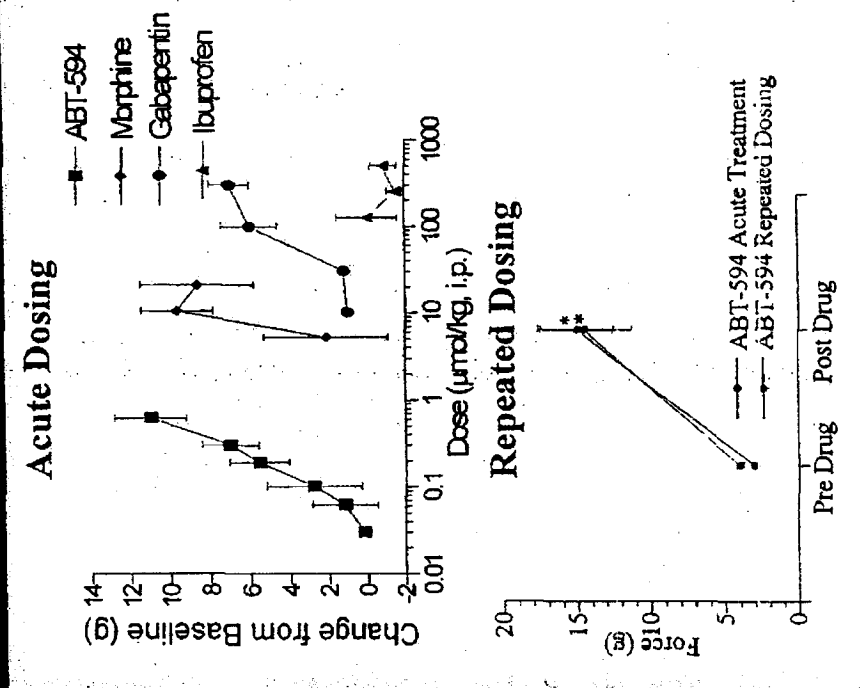


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ABBT 0002383

ABT-594: In Vivo Efficacy in Models of Neuropathic Pain

- ABT-594 exhibits comparable efficacy and enhanced potency vs. known efficacious agents in models of neuropathic pain
- Efficacy observed at ~ 3 ng/ml
- ABT-594 retains efficacy following repeated administration
- Efficacy observed in rodent model of diabetic polyneuropathy



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ABT-594: Efficacy vs. Other Analgesics

	Inflammatory Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 μ mol/kg)	+++ (0.1 μ mol/kg)	+++ (0.03 μ mol/kg)
Celecoxib	++ (30 μ mol/kg)	+ (30 μ mol/kg)	0
Morphine	+++ (3 μ mol/kg)	+++ (10 μ mol/kg)	++ (3 μ mol/kg)

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

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How do NNR Agonists Produce Analgesia?

- Mouse knockouts support role of $\alpha 4$ and $\beta 2$
 - Key differences between pain type
- Role for $\alpha 4$ subtype in acute thermal pain (activation of descending inhibitory pathways)
 - Antisense studies
 - Site injection studies
 - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

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ABT-594: Preclinical Assessment of Side Effect Liabilities

- Emesis
 - Emesis observed in monkey at 9x efficacious plasma levels
 - Emesis observed in dogs at efficacious plasma levels
 - Ferret model developed in response to early clinical data
 - Correlation established between activity at $\alpha 3\beta 4$ NNRs and emesis
- CV
 - No effects on hemodynamics at 30X efficacious plasma levels
- Dizziness: no validated preclinical models exist
 - Effects on balance, coordination and muscle strength (Edge Test) observed following acute but not repeated dosing
- ABT-594 displays a reduced propensity for morphine-like side effects of:
 - Constipation
 - Respiratory Depression
 - Sedation

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ABT-594: Summary of Preclinical Findings

- ABT-594 is effective across a broad range of preclinical models of acute, persistent and neuropathic pain
- ABT-594 retains efficacy upon repeated dosing
- The antinociceptive properties of ABT-594 are modulated via activation of NNRs and not via opioid receptors
- Preclinical studies suggest that ABT-594 will not exhibit morphine-like side effects of:
 - Constipation
 - Respiratory depression
 - Sedation
- Preclinical studies suggest that ABT-594 will have an improved side-effect profile relative to nicotine

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ABBT 0002388

**ABT-594 Project Review
February 2, 2001**

Clinical Overview

Bruce McCarthy

**HIGHLY
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ABBT 0002389

ABT-594

Take Home Messages

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
 - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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ABT-594

**Definitely NOT a take home
message for today:**

*ABT-594 will satisfy the unmet medical need
in pain management*

*A 2004 study published in the Journal of Pain
Management found that patients with chronic pain
who were treated with ABT-594 had a significantly
greater reduction in pain than those who were
treated with placebo.*

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ABBT 0002391

ABT-594

Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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ABBT 0002392

Classification of Pain

Pain Categories

Neuropathic

Acute

Post-dental & post-surgical Pain
Trauma
Pancreatitis
Infections

Chronic

Osteoarthritis
Rheumatoid arthritis
Fibromyalgia
Chronic visceral pain

Neuropathic

Acute

Compression neuropathy

Chronic

Diabetic polyneuropathy
Idiopathic polyneuropathy
Alcoholic polyneuropathy
Drug induced polyneuropathy
HIV predominantly sensory neuropathy
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
CRPS type I and II
Atypical facial pain
Phantom limb pain

Cancer pain
Back pain

Classification of Pain

Pain Epidemiology

• Chronic pain

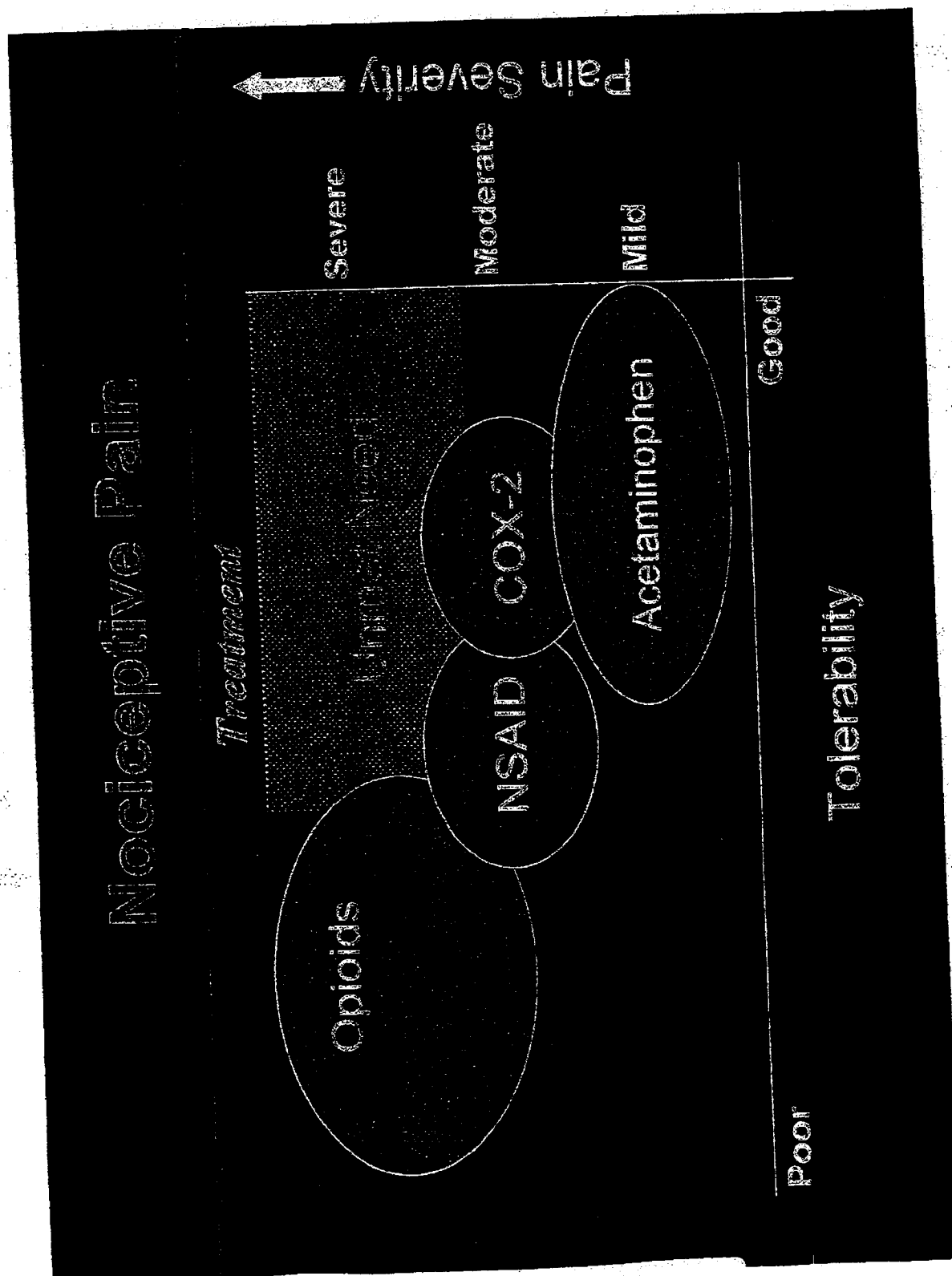
- 20% U.S. population: any chronic
- 22% worldwide: persistent pain

• Neuropathic pain

- 20% of diabetics
- 40% of HIV infected
- 36% of cancer

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ABIT 0002395

Nociceptive Pain

Treatment Adverse Events

OxyContin
Osteoarthritis
20 mg q12

OxyContin²

Ultram¹
50-100 mg

Event	Ultram ¹ 50-100 mg	OxyContin ²	OxyContin Osteoarthritis 20 mg q12
Somnolence	N/A	23 %	27 %
Dizziness	31 %	13 %	20 %
Nausea	34 %	23 %	41 %
Vomiting	13 %	12 %	23 %
Constipation	33 %	23 %	33 %
Pruritis	N/A	N/A	16 %

¹ Chronic non-malignant pain, up to 30 days (label)

² "Clinical trials" (label)

N/A - Not Available

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ABBT 0002396

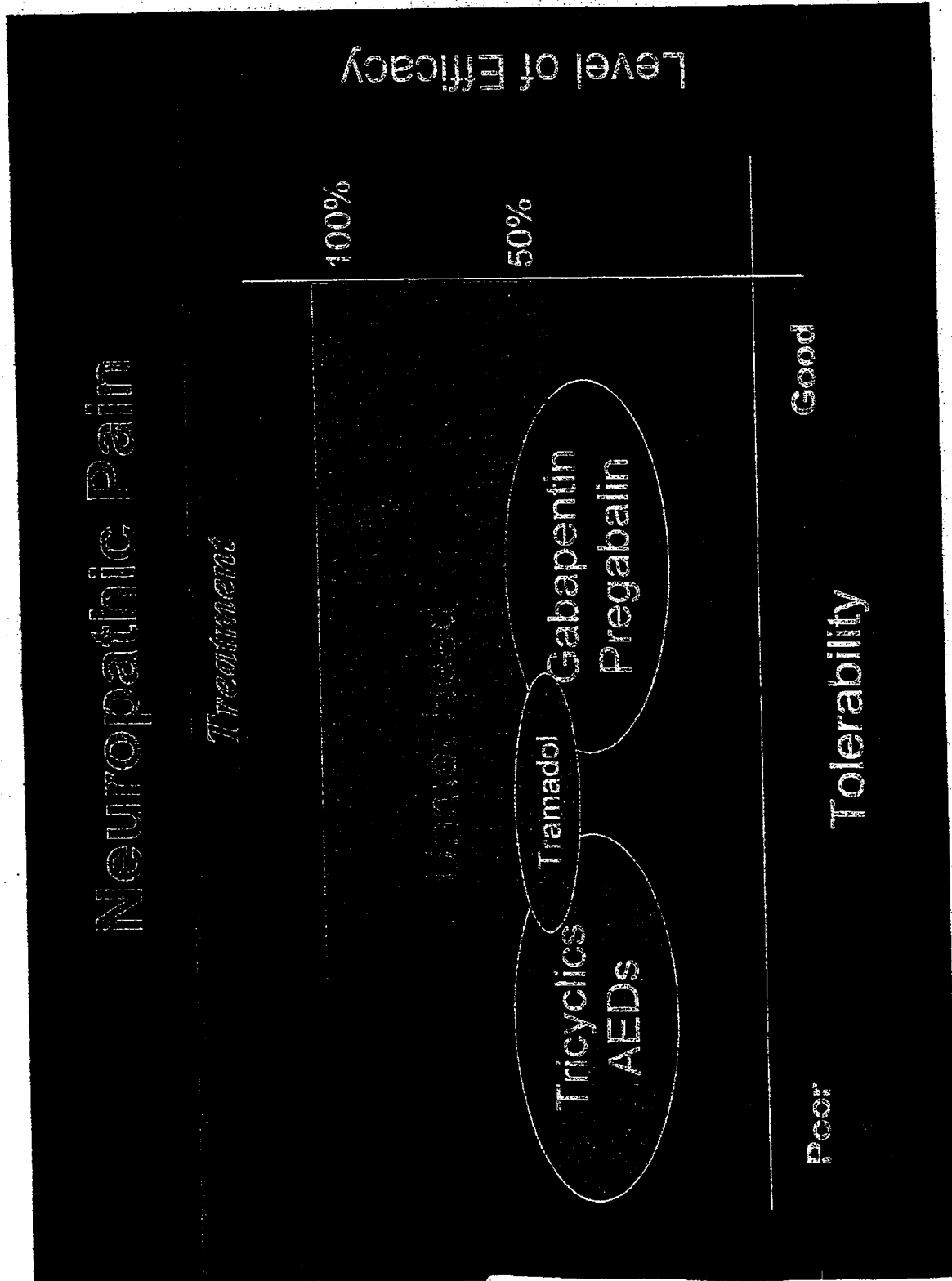
Neuropathic Pain

Overview

- Characteristic symptoms
 - Spontaneous: dysesthesia, shooting pains
 - Evolved: allodynia, hyperpathia
- Pathophysiology
 - Associated with peripheral nerve injury
 - Abnormalities develop over time in the PNS and CNS
- Treatment
 - Tricyclic and other "antidepressants"
 - Antiepileptic drugs
 - Sodium channel blockers (lidocaine)
 - Opioids
 - All minimally effective

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ABBT 0002398

Neuropathic Pain

Treatment Adverse Events Rates

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A		
Somnolence	66%	N/A	6%	5%
Dizziness	28%	56%	23%	24%
Nausea	N/A	40%	24%	37%
Peripheral edema	N/A	7%	8%	N/A
Dry mouth	20%	N/A	N/A	73%
Instability	N/A	N/A	N/A	N/A
		13%	N/A	N/A
			N/A	N/A

¹ Max, 1987 (n=20)
N/A - Not Available

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ABBT 0002399

ABT-594

Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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ABBT 0002400

ABT-594

Proof of Principle

What characterizes an innovative analgesic?

Spectrum of activity

Time of onset/duration

Level of efficacy

Safety/efficacy ratio

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ABBT 0002401

ABT-594

Spectrum of Activity: Where to Start?

Acute

Post-dental surgery
Sprains and strains
Acute back pain
Trauma
Post-general surgery
Post-orthopedic surgery
Dysmenorrhea
Renal colic
Biliary colic
Pancreatitis
Infections

Neuropathic

Diabetic polyneuropathy
Idiopathic polyneuropathy
Alcoholic polyneuropathy
Drug-induced polyneuropathy
HIV predominantly sensory neuropathy
Back pain
Cancer pain
Trigeminal neuralgia
Post-herpetic neuralgia
Thalamic pain syndromes
Spinal cord injury
Multiple sclerosis
Complex regional pain syndromes (I, II)
Atypical facial pain
Phantom limb pain

Chronic Nociceptive

Osteoarthritis
Chronic back pain
Rheumatoid arthritis
Cancer pain
Fibromyalgia
Sickle cell disease
TMJ disorder
Bursitis
Teninitis
Chronic visceral pain

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ABBT 0002402

ABT-594

Choose Portals of Entry

Molar
Extraction

Acute Pain



Peripheral
Neuropathy

Neuropathic Pain



Osteoarthritis

Chronic Nociceptive
Pain



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ABET 0002403

ABT-594

Initial Profile

- **Preclinical promise**

- Efficacy for all types of pain
- Challenges

- **Current characteristics**

- Analgesic potential demonstrated in molar extraction, neuropathic pain and osteoarthritis
- Onset (T_{\max} , tolerability) appears to exclude rapid relief of pain (“acute pain”)

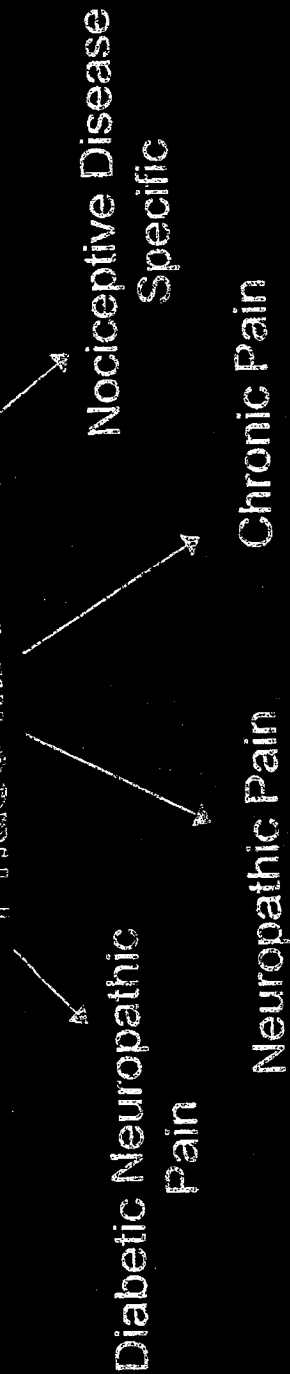
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ABBT 0002404

ABT-594

Future Regulatory Strategy

Phase IIb Results



+/- Publication Strategy/Phase IV (e.g.)

- Post-herpetic neuralgia
- Nociceptive pain
 - o Osteoarthritis
 - o Low back pain

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ABT 0002405

ABT-594

Clinical development

- Current pain management
- Development strategy: bench to bedside
- Clinical trial results

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ABT 0002406

ABT-594

Pharmacokinetics and Metabolism

- Half-life ($t_{1/2}$): about 8-12 hours
- Dose proportional kinetics
- AUC, C_{max} similar across formulations (solution, SEC, HGC)
- AUC, C_{max} similar with/without food
- T_{max} varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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ABBV 0002407

ABT-594

ABT-594's analgesic potential demonstrated in:

Molar Extraction

Neuropathic Pain

Osteoarthritis

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ABB 0002408

Molar Extraction Study

Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo
Single dose	

- Third molar extraction

- Outcome measures:

Pain relief (PR)

Categorical scale:

0	1	2	3	4
none	a little	some	a lot	complete

- Power: 70% to detect an effect similar to acetaminophen plus codeine Solution

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ABBT 0002409

Molar Extraction Study

Outcome Measures

Pain Relief (PR)

Categorical scale: 0 none 1 a little 2 some 3 a lot 4 complete

Total Pain Associated Relief (TOTPAR)

Area under the curve for PR (0-6 hours)

Pain Intensity (PI)

Categorical scale: 0 none 1 mild 2 moderate 3 severe

Visual Analog Scale

no pain | worst pain

Stop Watch Model

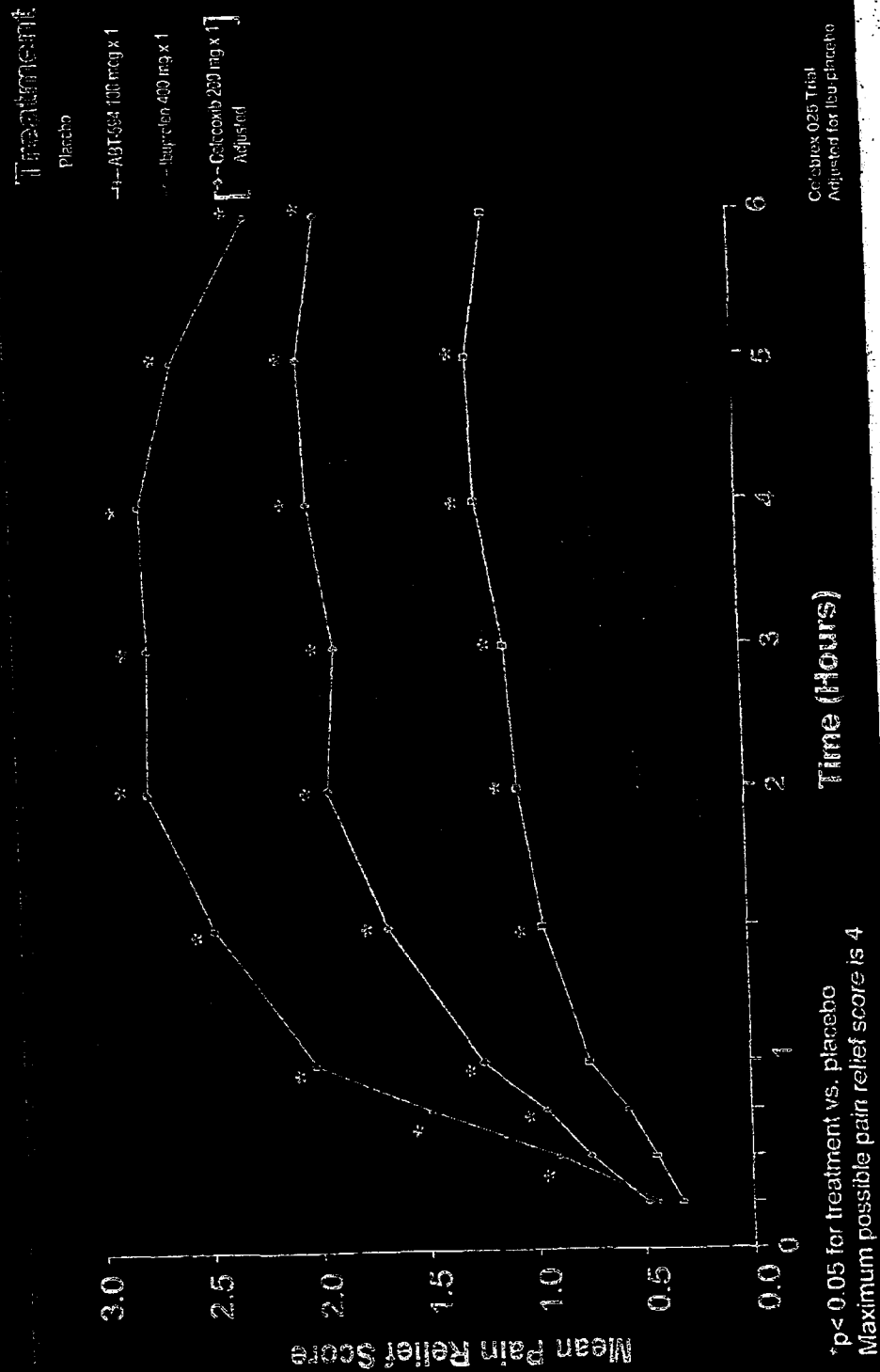
Time to "perceptible" and "meaningful" relief

Time To Rescue Medication

Patient Global

Rate medication: 1 poor 2 fair 3 good 4 excellent

ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



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ABBT 0002411

McCarthy Deposition Exhibit 37

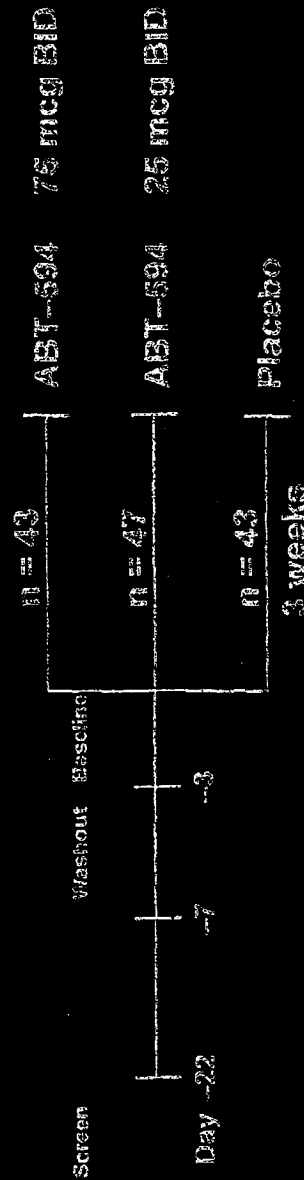
P's Exhibit EL

Part 3

Neuropathic Pain Pilot

Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
 - 52% idiopathic
 - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

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ABBT 0002412

Neuropathic Pain Pilot

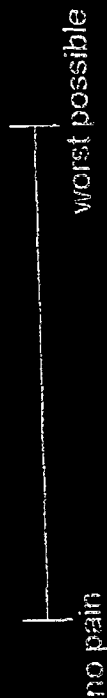
Outcome Measures

• Pain Intensity (PI)

-- Categorical Scale:

0 none 1 mild 2 moderate 3 severe

-- Visual Analog Scale:
(0-100 mm)



• Neuropathic Pain Scale (NPS)

-- 10 items (e.g., sharp, hot, intense), for total 0-100 points

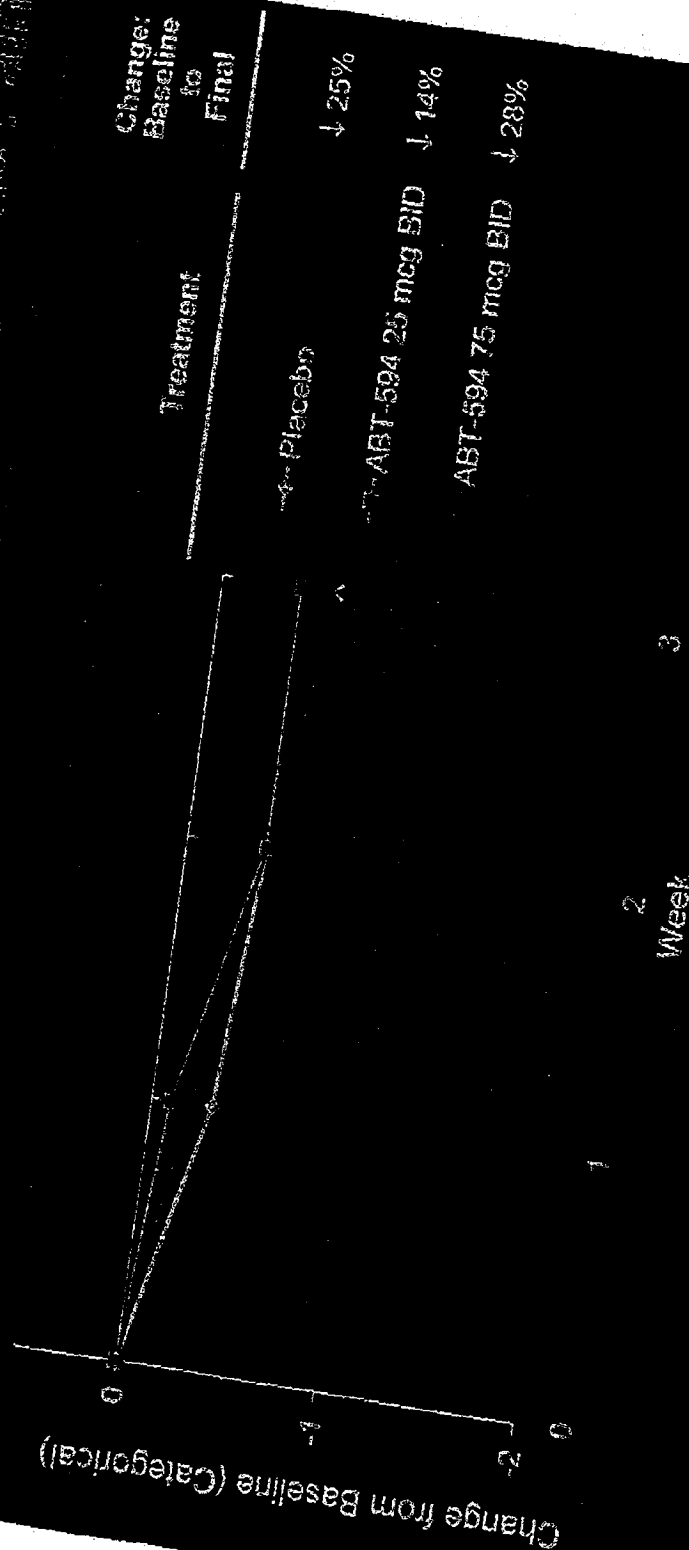
Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10	The most sharp sensation imaginable ("like a knife")
-----------	---	---	---	---	---	---	---	---	---	----	--

• Patient Global (PG)

-- Rate Medication:

1 poor 2 fair 3 good 4 excellent



Maximum possible decrease for 75 mcg BID was 2.5

Model based, ITF
 1000
 1000

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ABBT 0002414

ABT-594 75 mcg BID Reduces the NPS More Than Placebo

Change:
Baseline
to
Final

Treatment

↓ 21%

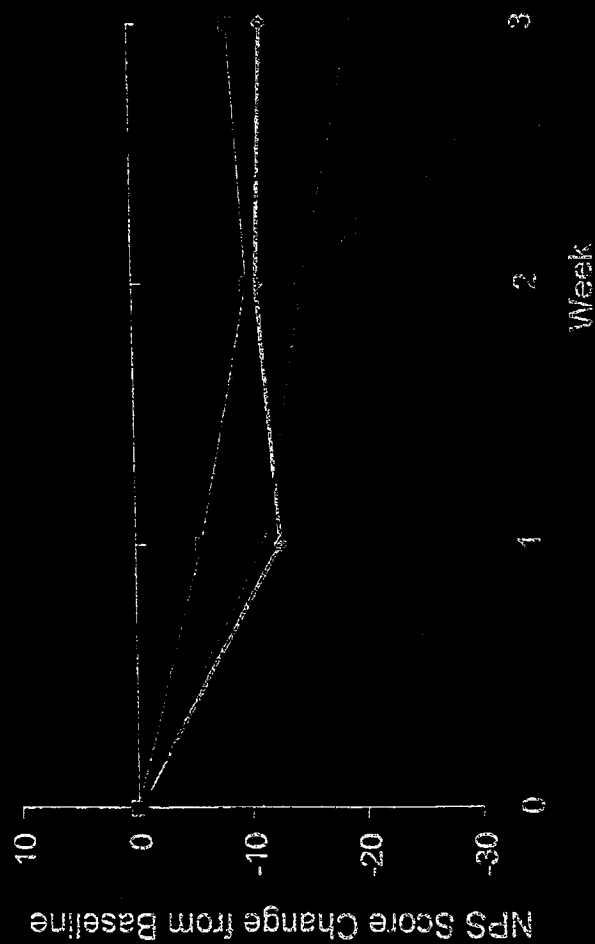
↓ 19%

↓ 36%

Placebo

ABT-594 25 mcg BID

ABT-594 75 mcg BID



Maximum possible decrease for 75 mcg BID was 59

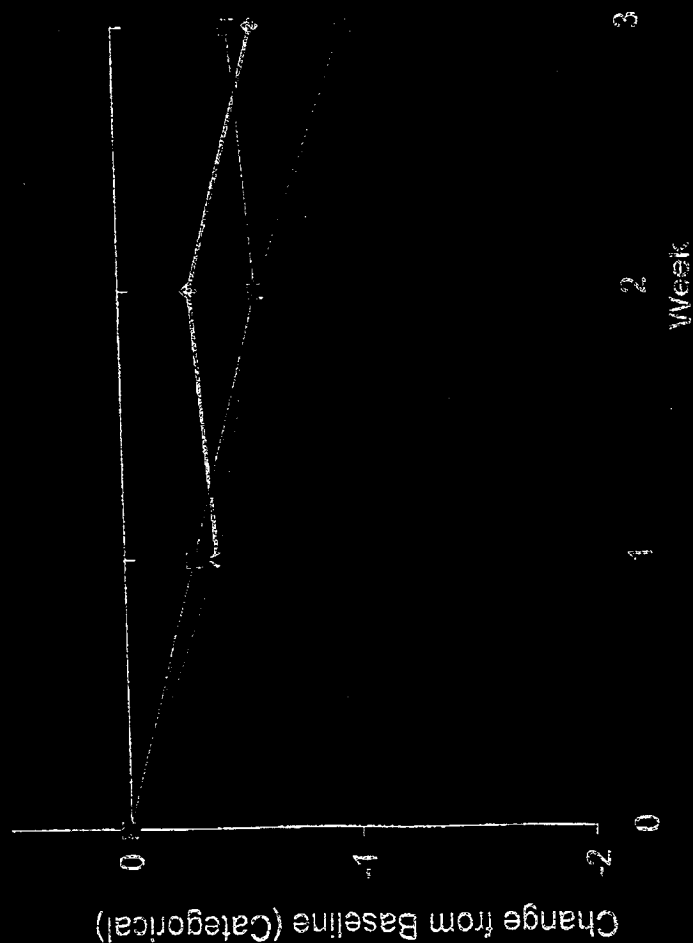
Model Based, ITT
LOCF
833

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ABBT 0002415

ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy

Treatment	Change: Baseline to Final
Placebo (n=24)	↓ 25%
ABT-594 25 mcg BID (n=18)	↓ 22%
ABT-594 75 mcg BID (n=17)	↓ 38%

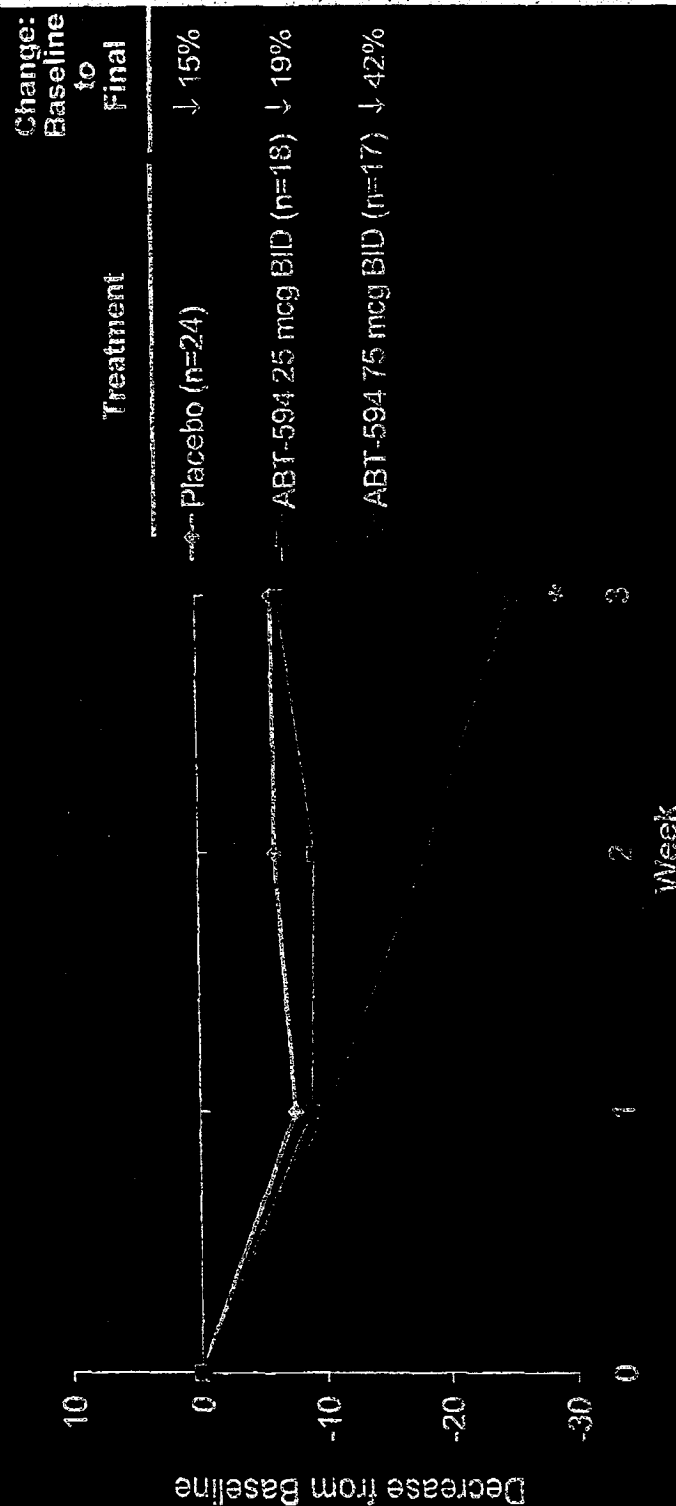


Placebo based, ITT
LOCF
833

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ABBT 0002416

ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy



Merck Brand, ITT
LOCF
933

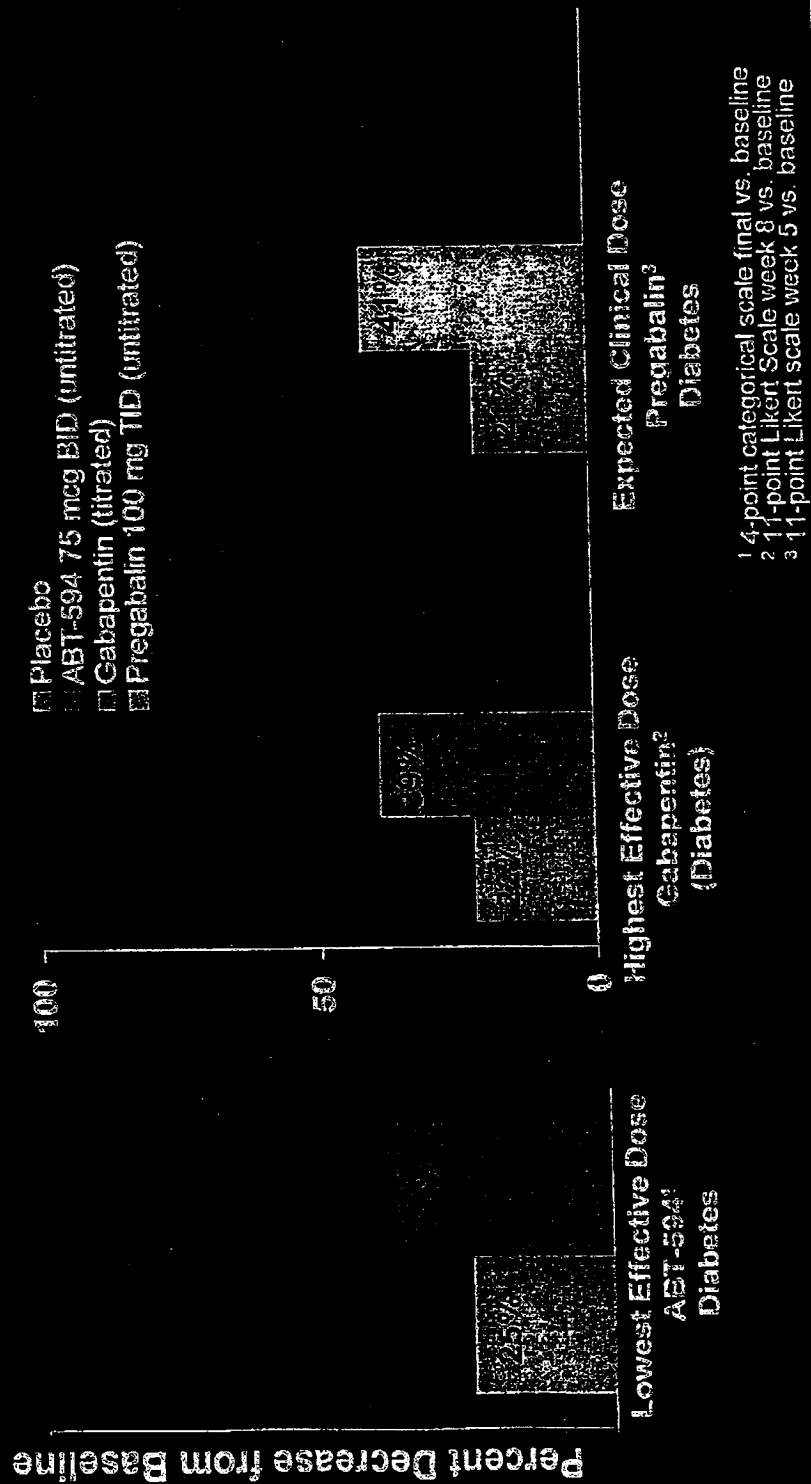
* $p < 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 52

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ABBT 0002417

ABT-594 75 mcg BID has a Similar Effect To Gabapentin

ABT-594 vs. Gabapentin and Pregabalin



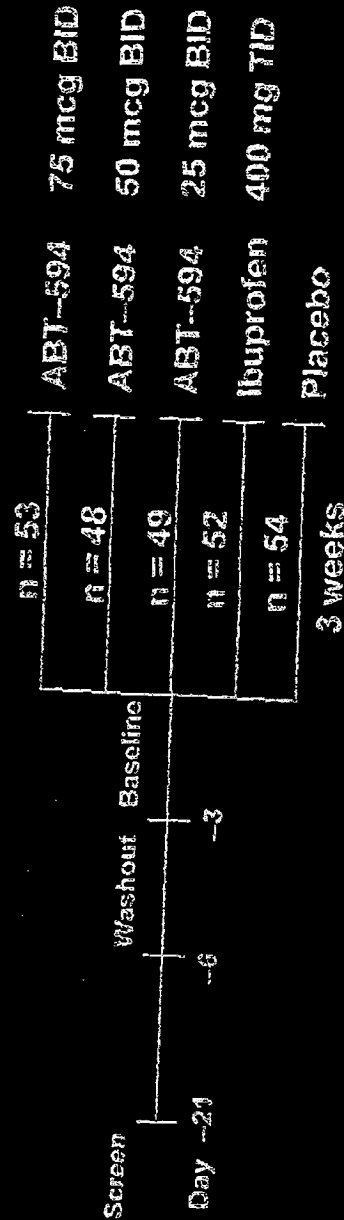
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ABBT 0002418

Osteoarthritis Pain Pilot

Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)

- Soft Elastic Capsule

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ABBT 0002419

Osteoarthritis Pain Pilot Study

Outcome Measures

Pain Intensity (PI)

– Categorical Scale:

0	1	2	3
none	mild	moderate	severe

– Visual Analog Scale (VAS):



WOMAC

- Pain (0-500)
- Stiffness (0-200)
- Function (0-1700)

Total (0-2400)

Patient Global

– Rate Medication:

1	2	3	4
poor	fair	good	excellent

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ABBT 0002420

Osteoarthritis Pain Pilot Study

WOMAC

Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain |

| extreme
pain

Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness |

| extreme stiffness

Function

What degree of difficulty do you have...

- Descending stairs?
- Rising from bed?

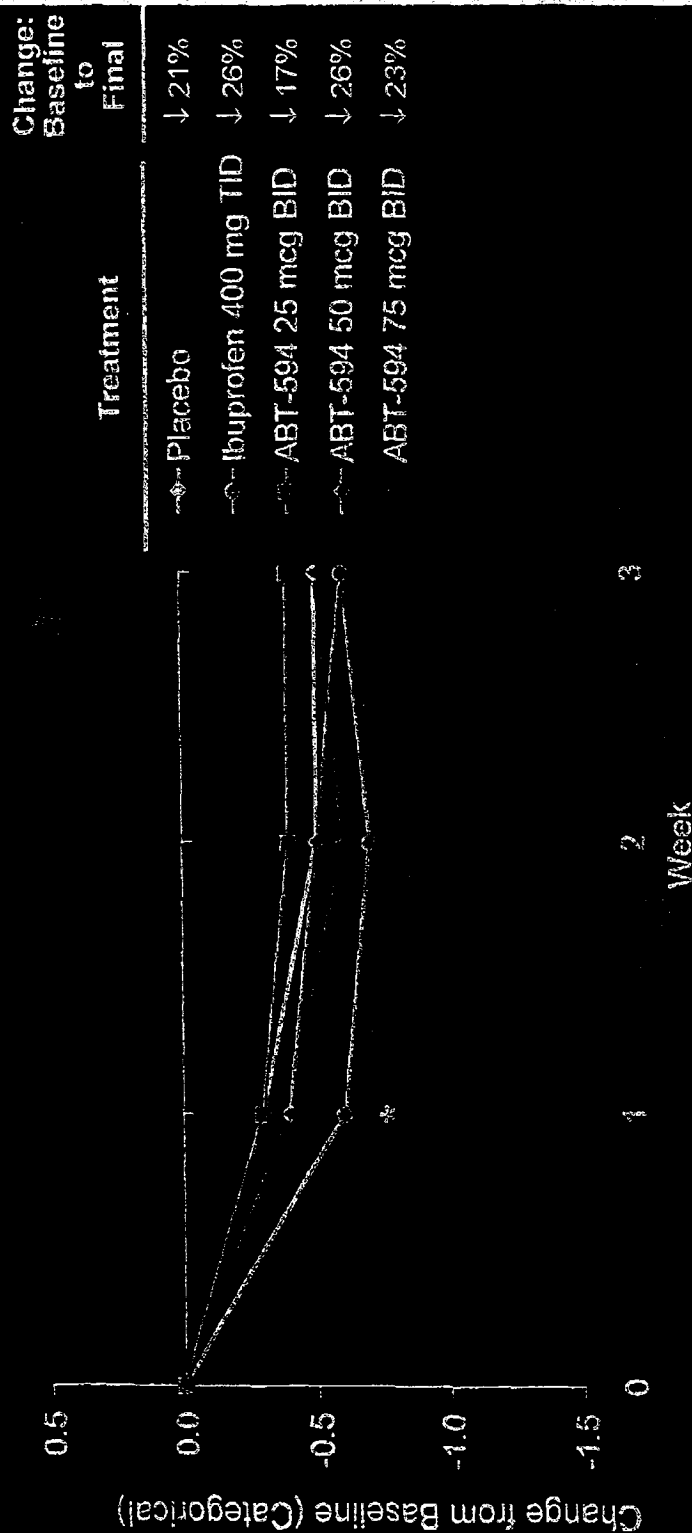
no difficulty |

| extreme difficulty

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ABBT 0002421

ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis



Model based, ITT
LOCF
825

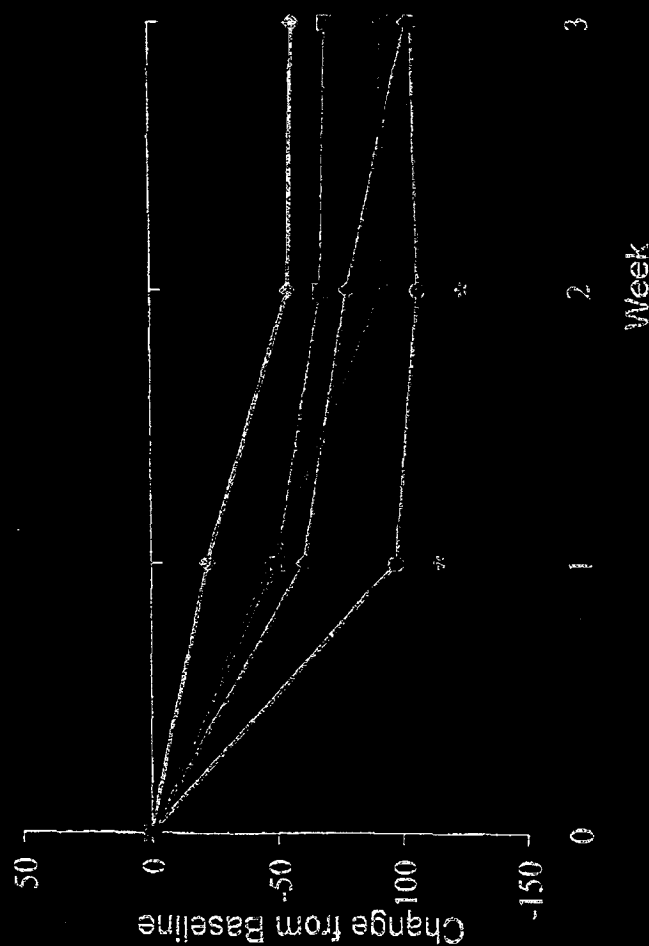
* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 2.2

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ABBT 0002422

ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis

Treatment	Change: Baseline to Final
Placebo	↓ 19%
Ibuprofen 400 mg TID	↓ 33%
ABT-594 25 mcg BID	↓ 24%
ABT-594 50 mcg BID	↓ 34%
ABT-594 75 mcg BID	↓ 30%



* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 305

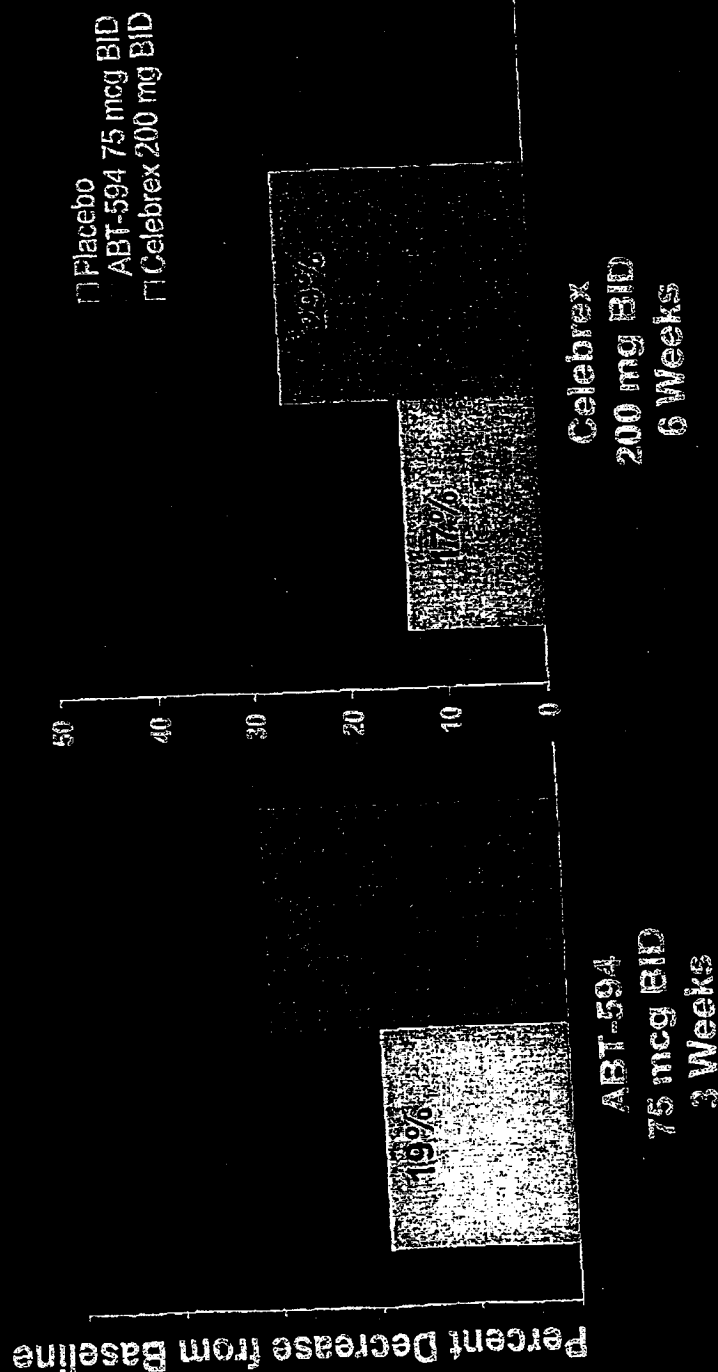
Based on 5-item (0-500 points)

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ABBT 0002423

ABT-594 75 mcg BID Has An Effect Similar to Celebrex

WOMAC Pain Decrease from Baseline



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ABBT 0002424

ABT-594

Phase IIIa Efficacy Conclusions

• Analgesic Potential Demonstrated

• Molar Extraction

- Significance vs. placebo starting at 1.5 hours

• Neuropathic Pain

- 75 mcg BID may be lowest effective dose for patients with painful diabetic polyneuropathy

• Osteoarthritis Pain

- 75 mcg BID may be lowest effective dose as judged by the WOMAC pain sub-score

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ABT-594 Safety

Phase III Adverse Events

• Characteristic AEs

- Nausea

- Vomiting

- Dizziness

- AEs attenuate after repeated administration

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ABT 0002426

Adverse Event Rates for Select Analgesics

Event	Anitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 ² 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	23%	0%
Dizziness	23%	40%	24%	23%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	4%
Constipation	14%	N/A	N/A	N/A	N/A
Day tired	99%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	N/A

¹ Max, 1987 (n=29)

² M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002427

Adverse Event Rates for Select Analgesics

Event	Ultram ¹ 50-100 mg q4-6h	OxyContin ²	OxyContin Osteoarthritis 20 mg q12h	ABT-594 ³ 75 mcg BID
Somnolence	N/A	23%	27%	0%
Dizziness	31%	13%	20%	7%
Nausea	34%	23%	44%	15%
Vomiting	15%	12%	23%	5%
Constipation	38%	23%	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

¹ Chronic non-malignant pain, up to 30 days (label)

² "Clinical trials" (label)

³ M98-826 and M98-833 combined

N/A - Not Available

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ABBT 0002428

ABT-594

Phase IIa Conclusions

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
 - SEC tolerated better than predicted by solution
 - 75 mcg BID (HGC) very well tolerated vs. other analgesics
 - Two Phase I studies (M99-076 and M99-120) showed:
 - 300 mcg BID HGC tolerated
 - Titration may improve tolerability
- Full analgesic potential should be defined with adequate dose ranging studies in Phase IIb

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Phase IIIb

- Trials

- Neuropathic Pain (M99-114)

- Ongoing

- Osteoarthritis Pain (M99-115)

- Unfunded

- Doses

- 150, 225, 300 mcg BID

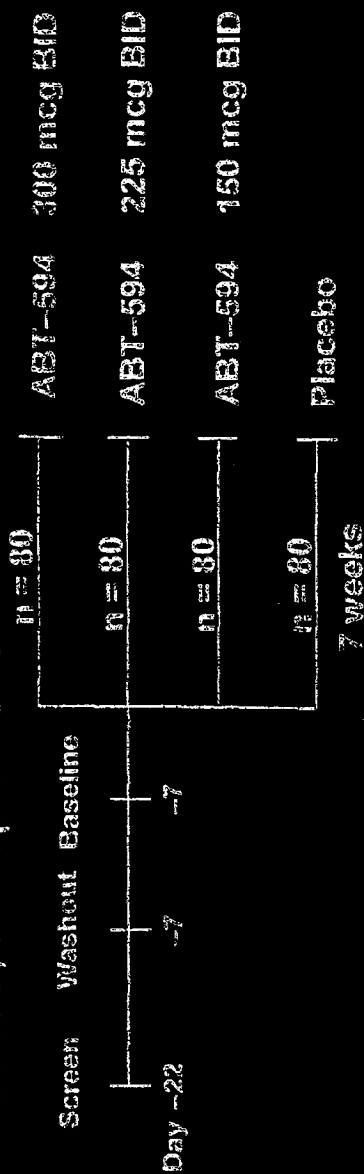
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ABBT 0002430

M99-114: Neuropathic Pain

Design

- 320 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-Day primer phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)
- Hard Gelatin Capsule

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ABBT 0002431

M99-114: Neuropathic Pain

Outcome Measures

• Primary

- Weekly average of daily pain (11-point Likert in a diary)

• Secondary

- Site-based pain scale (11-point Likert)
- Neuropathic Pain Scale
- Patient Global Impression of Change
- Physician Global Impression of Change
- SF-36

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ABBT 0002432

M99-114 Status

Enrollment

- Ended 1/5/01 at 269 subjects
- Pre-specified power not reached
- Width of confidence intervals not meaningfully different between 269 and 320 enrolled

Database release - 5/01

Go/No Go - 6/01

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ABBT 0002433

ABT-594

Take Home Messages

1. Significant unmet needs in pain management
2. Prior studies: potential of ABT-594 to address these unmet needs
3. Ongoing study: test the hypothesis that ABT-594 addresses unmet need in neuropathic pain
 - A proposed study would do the same for chronic nociceptive pain
4. There is a process by which we will determine if ABT-594 can satisfy the unmet need

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ABBT 0002434

**ABT-594 Project Review
February 2, 2001**

Commercial Assessment

Andrea Landsberg

Laura Robinson

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ABBT 0002435

ABT-594 Commercial Assessment: Key Take Aways

- Neuropathic pain market is the primary target
 - Underserved market with significant unmet need
 - ABT-594 has potential to be first novel drug in decades indicated for neuropathic pain
- Additional opportunity in “chronic persistent pain” market
- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*

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Neuropathic Pain Market Sales

	2000 US Sales (\$MM)	2000 ex-US Sales
AEDs	\$299	\$190
TCAs	\$3	\$45
OPIOIDS	\$37	NA
OTHERS	\$85	\$45
TOTAL	\$424	\$280

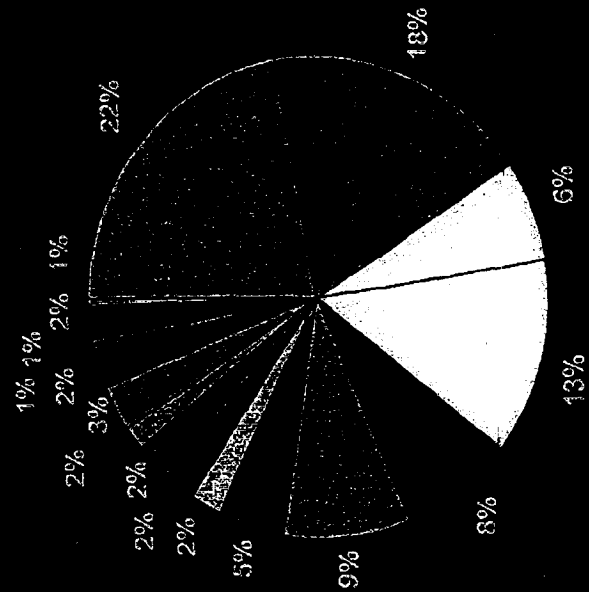
US Sales factored for neuropathic pain and annualized
Vs Prior Year: US Growth est 20%, ex-US growth est 10%

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ABBT 0002437

Drug Classes Used to Treat Neuropathic Pain

*Dispersed market due to limited promotion
and lack of dominant effective product*



Drug Uses Data (not Rx or \$'s)

SEIZURE DISORDERS
ANTIARTHRCS SYS PLN
COX-2 INHIBITORS
CODEINE & COMB NON-INJ
CORTICIDS PLAIN INJ
ANTIDEP TR/TETRA
PTY ANALGESICS
PYRIDOXINE (VIT B6)
SYN NON-NARC NON-INJ
MUSC RLX W/O ANALG
CORTICIDS PLAIN ORAL
PROPOXYPHENES
ANESTH INJECT LOCAL
ASPIRIN, APC, ETC
SSRI'S/SNRI'S
ACETAMINOPHEN
BENZODIAZEPINES

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ABBT 0002438

Use in Neuropathic Pain

- Even if target only 'focused' indication in 'painful, diabetic neuropathy' expect trial and usage in all types of neuropathic pain
 - Neurontin use all off-label
 - Carbamazepine is indicated for trigeminal neuralgia but used in all neuropathic pain
 - Generally held premise that NP likely has some similar mechanisms across etiologies (reinforced by current drug usage)

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ABBT 0002439

McCarthy Deposition Exhibit 37

P's Exhibit EL

Part 4

Market Opportunities in Neuropathic Pain

- Improved efficacy
 - Partial pain relief is the norm
 - Polypharmacy often required to manage pain
- Improved responder rates
 - Typically only 40% to 60% of patients respond to any given treatment
- Improved tolerability over time
 - TCAs, AEDs, opioids have troublesome SEs that do not diminish over time
- Dose reduction
 - Most TCAs and AEDs (including Neurontin) typically dosed TID
- Titration reduction
 - TCAs and AEDs require >2 weeks titration period to minimize SEs or reach effective dose

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ABBT 0002440

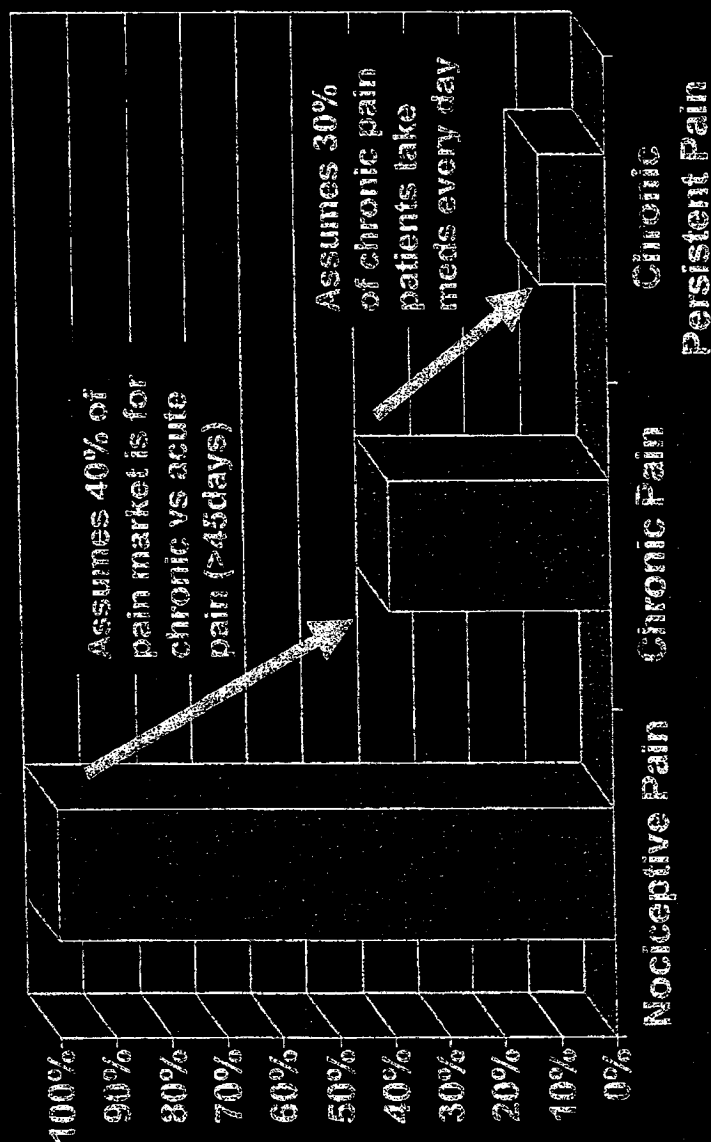
Chronic Persistent Pain (CPP) "Spillover"

- Onset of action and need for titration limits ABT-594 to a small segment of the nociceptive pain market
- CPP = Chronic persistent pain conditions for which patients are on daily medications, over extended periods of time (vs. PRN, or 'as needed', consumption)

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ABBT 0002441

Chronic Persistent Pain



IMS Longitudinal Data indicates over 80% of pain meds Rxed for >=30 days
Quantitative primary market research indicates that >60% of chronic pain patients take meds every day

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ABBT 0002442

Chronic Persistent Pain Market

	1999 Sales (\$MM)	CAGR (97-99)	Rxs (MM)	CAGR (97-99)
US	\$700	5%	35	1%
Ex-US	\$680	3%	58	3%

CPP Market Size Assumptions:

Assume 40% of opioid, non-opioid, COX-2 market is for chronic pain and 30% of that is 'persistent', i.e.: medication taken every day

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ABBT 0002443

Qualitative Market Research Results

Profile			Share of Patients		
Efficacy	AEs vs. current agents		OA	RA	Low-back

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

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ABBT 0002444

Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent			
Same	Equivalent			
Better	Poor			

TGAs used as "benchmark" efficacy in NP

Tolerability vs. current agents: equivalent = 5% nausea; 5% vomiting; 10% dizziness; poor = 20% nausea; 10% vomiting; 30% dizziness

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Qualitative Market Research Results

<u>Profile</u>		<u>Share of Patients</u>		
Efficacy	AEs vs. current agents	OA	RA	Low-back
Better	Equivalent	19%	12%	16%
Same	Equivalent	15%	8%	10%
Better	Poor	12%	6%	11%

Spillover market share in chronic persistent pain markets (in forecast, assuming only 5% share)

MR did not test impact of titration on market share

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Qualitative Market Research Results

Profile		Share of Patients
Efficacy	AEs vs. current agents	Neuropathic Pain
Better	Equivalent	31%
Better	Poor	24%
Same	Equivalent	27%

Assumes ABT-594 is indicated for NP, with additional clinical data (Ph II) showing efficacy in nociceptive pain

In forecast assuming 20% share of NP

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Neuropathic Pain Pipeline

- Pregabalin is in Phase III, but questions remain regarding Pfizer's Neurontin/Pregabalin strategy
- 4 NMR preclinical programs appear to be targeting pain indications; ABT-594 is much further along
- Other new AEDs may have potential for treatment of neuropathic pain and are conducting phase IV trials; unclear whether these agents will pursue an NP indication
- Several novel pain mechanisms being explored
 - Calcium channel blockers
 - Sodium channel blockers
 - NMDA antagonists

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Positioning of ABT-594 in Neuropathic Pain

- Greater efficacy than AEDs and TCAs in NP
- Better long term tolerability (than TCAs and opioids)
- Safe in all patient populations
- Convenient BID dosing with simple, short titration period
- No tolerance over time and non-scheduled
- Limited drug interactions
- Novel mechanism of action

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Positioning of ABT-594 in CPP

- Effective alternative to opioids with:
 - No tolerance, respiratory depression, constipation, etc.
 - Non-scheduled
- For patients receiving insufficient relief with current therapies or NSAID/opioid intolerant patients
- Better efficacy than COX-2s with novel mechanism of action and no major safety issues

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ABT-594 Global Forecast Ranges

(\$MM)

	Peak Sales		
	Low	Base	High
US	\$92	\$339	\$509
Ex-US	\$130	\$363	\$712

- NP shares: 5%, 20% or 30%
- CPP shares: 3%, 5%, 7%

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ABBT 0002451

Key Product Challenges

- *Key challenge is achieving optimal balance of tolerability and efficacy to satisfy both US and ex-US markets*
- Neurontin/Pregabalin may have advantage
 - Will need to minimize early DCs as much as possible
- Potentially low therapeutic index
- Titration
- Schedule must be as short and simple as possible
- Nicotinic mechanism
- Will require pre-launch market education and priming to diffuse negative associations and generate interest surrounding novel MOA

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ABBT 0002452

Go/No Go Process

Bruce McCarthy

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ABBT 0002453

ABT-594

Go/No Go Process

The Challenge

Integration of many interrelated data

Efficacy

Safety

Dose Response

Pharmacodynamics

Dose Selection

Phase III Trial Design

Titration Effects

Indications

Market Research

Segmentation

Targeting

Positioning

The Plan

Leverage decision analysis (DSG) as a process
to determine Go/No Go criteria

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ABT-594

Go/No Go Process

Process to include:

1. Scope and frame issues and process
2. Analysis of M99-114 and other clinical data
3. Dose identification
4. Draft Phase III trial design
5. Market research
6. Valuation
7. Presentation and asset strategy: 6/01

Decision Analysis

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ABT-594

Go/No Go Process

What will a "Go" decision look like?

Patients and physicians will have
compelling reasons to choose ABT-594 vs.
other analgesics for the relief of pain

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ABT 0002456

**ABT-594 Project Review
February 2, 2001**

Follow-On Strategy

Mike Meyer

**HIGHLY
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ABBT 0002467

Identification of ABT-594 Backup

Clinical Results Outline Specific Improvements Required for Backup

- Emesis
 - Modeled preclinically in ferret and dog
- Nausea
 - Ferret model can qualitatively address nausea index
- Dizziness
 - Mouse rotarod
 - Rat Edge test

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ABBT 0002458

Discovery Program Basis

NNR Subtypes Differentially Mediate Efficacy and Side Effects

- Different NNR subtypes mediate analgesic effects of nicotinic agonists and adverse events
- Program committed to the identification of NNR subtype selective compounds
- Project initiated research collaboration with NeuroSearch (Denmark)
 - Access to human recombinant NNRs
 - Access to new structural classes of NNR modulators

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ABBT 0002459

Nociception Mediated by $\alpha 4$ Subtypes

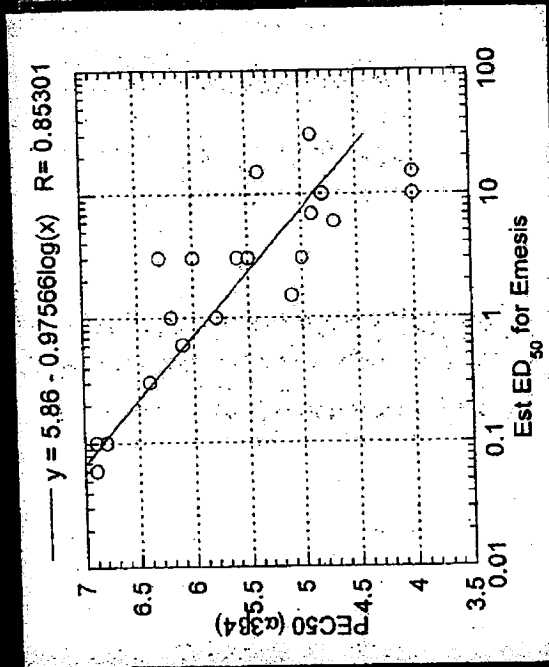
- Mouse knockouts support role of $\alpha 4$ and $\beta 2$
 - Key differences between pain type
- Role for $\alpha 4$ subtype in acute thermal pain (activation of descending inhibitory pathways)
 - Antisense studies
 - Site injection studies
 - Antagonist studies
- In more physiological relevant models of persistent and neuropathic pain, both central and peripheral sites of action are implicated

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Emesis Mediated by $\alpha 3 \beta 4$ Subtype

- In preclinical models, emesis is correlated to potency and efficacy at ganglionic ($\alpha 3 \beta 4$) NNR subtypes
- Antagonist and route of administration studies suggest both local and systemic contribution



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ABBT 0002461

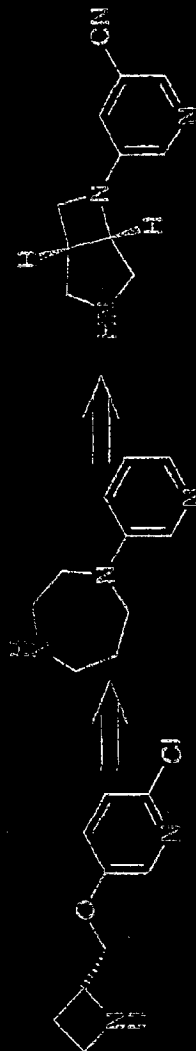
α 4-Selective Ligands: In Vitro Profile

• Radioligand Binding Profile:

0.046 nM

0.049 nM

3.19 nM

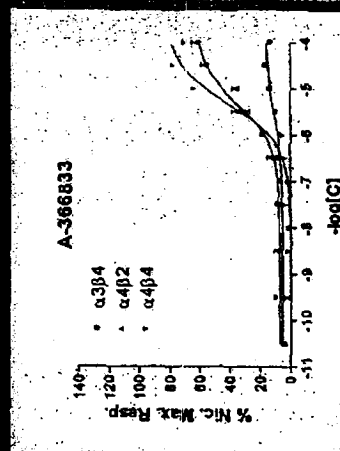
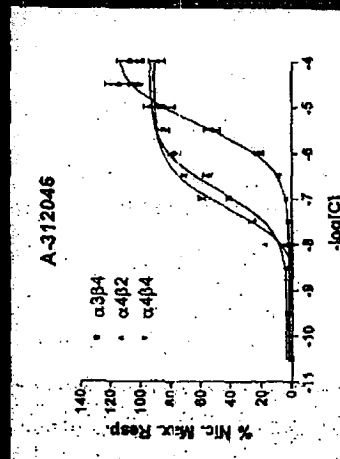
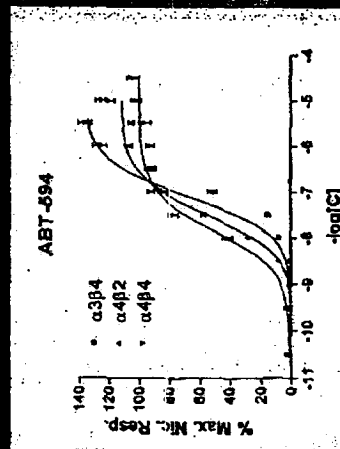


ABT-594

A-312046

A-366833

• In Vitro Functional Profile:

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ABBT 0002462

Analgesic Efficacy vs. ABT-594 (Rat Models)

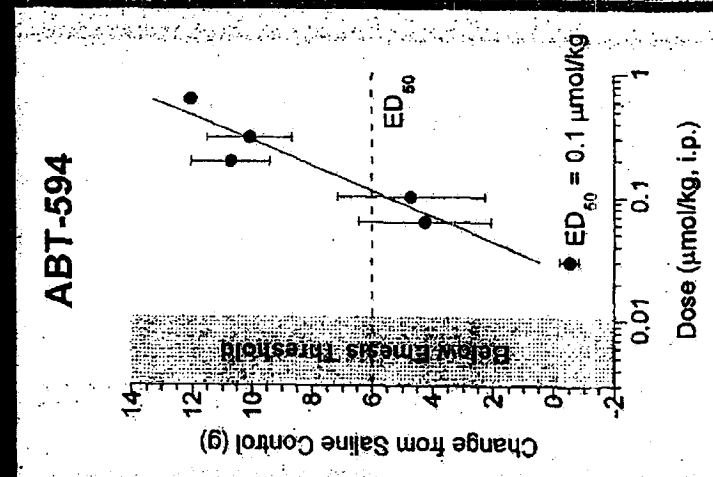
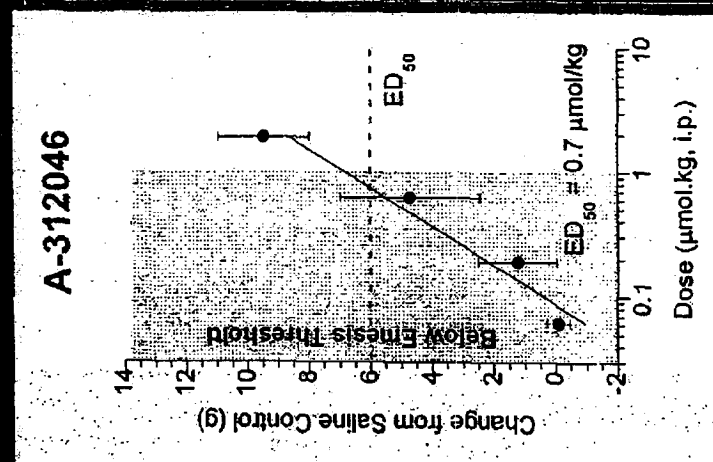
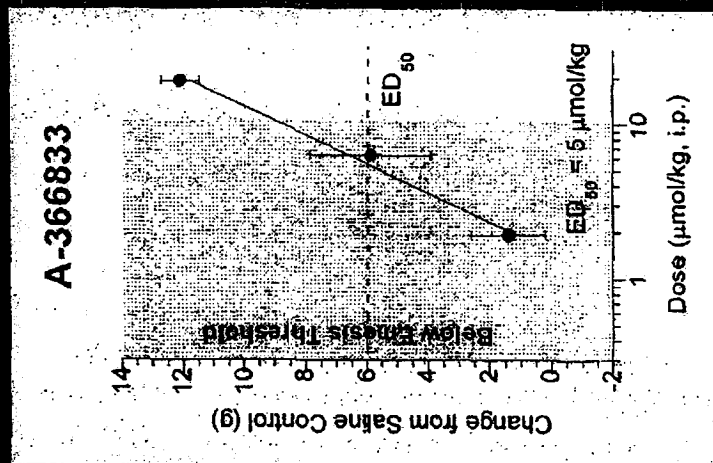
	Persistent Nociceptive Pain (Formalin Model)	Neuropathic Pain (Chung Model)	Acute Nociceptive Pain (Hot Box)
ABT-594	+++ (0.08 μ mol/kg)	+++ (0.1 μ mol/kg)	+++ (0.03 μ mol/kg)
A-312046	+++ (1.8 μ mol/kg)	+++ (0.7 μ mol/kg)	+++ (1.9 μ mol/kg)
A-366833	+++ (3 μ mol/kg)	+++ (5 μ mol/kg)	++ (6 μ mol/kg)
Celecoxib	++ (30 μ mol/kg)	+	0
Morphine	+++ (3 μ mol/kg)	+++ (10 μ mol/kg)	++ (3 μ mol/kg)
Gabapentin	+	++ (100 μ mol/kg)	0

+++ is >75% efficacy; ++ is 40-75% efficacy; + is <40% efficacy; 0 is no activity.

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ABBT 0002463

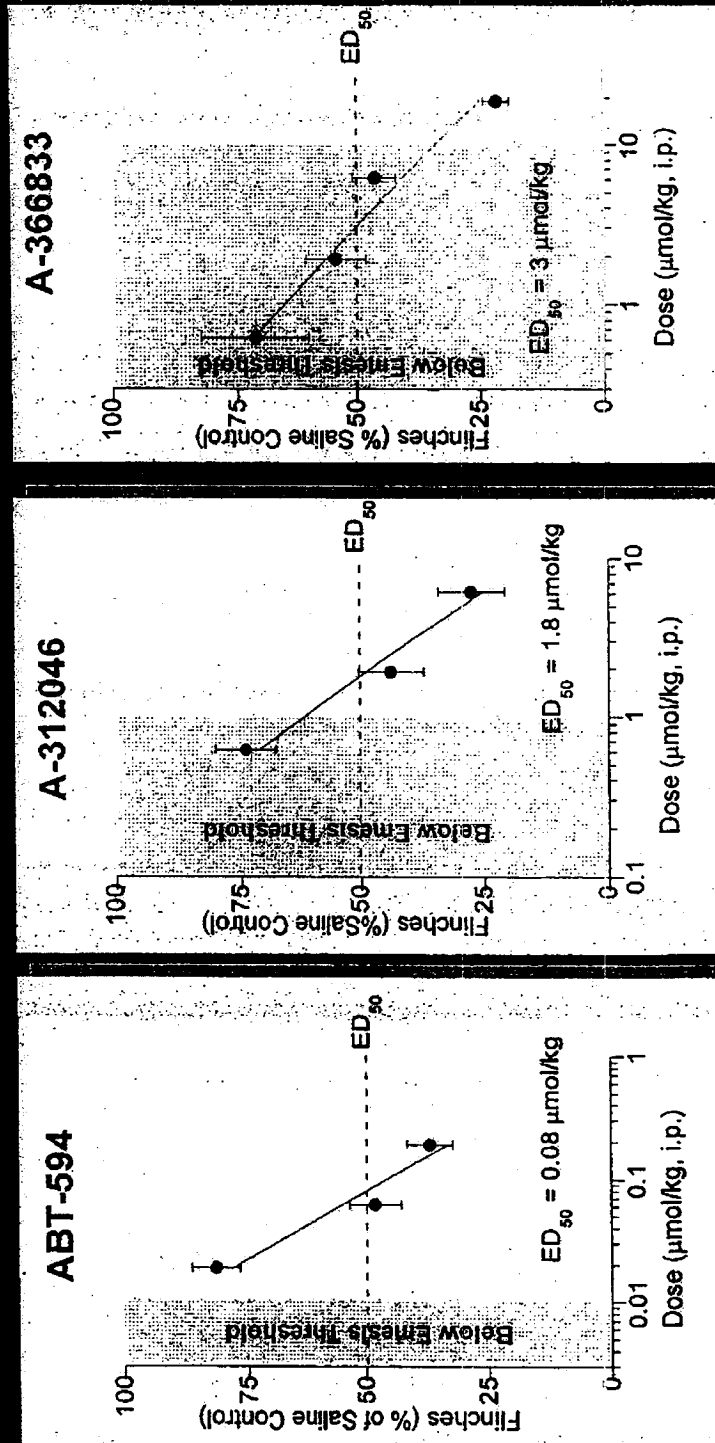
Efficacy Indexed to Emesis Liability (Neuropathic Pain)



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ABBT 0002484

Efficacy Indexed to Emesis Liability (Nociceptive Pain)



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ABBT 0002466

Therapeutic Index Comparison

Therapeutic index based on ratio of highest no effect dose for adverse event and ED₅₀ in pain models

Adverse Event	Therapeutic Index Improvement vs. ABT-594	
	A-312046	A-366833
Emesis (Ferret)	5 - 14x	20 - 27x
Seizure Threshold (Mouse)	4 - 11x	>11x
Edge Test (Rat)	7 - 24x	>12x

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Pharmacokinetics

	$t_{1/2}$	CLp	%F
Rat	1.5 h	1.7	51%
Dog	4.7 h	0.4	35%
Monkey	1.4 h	1.7	90%
Rat	3.0 h	1.95	80%
Dog	1.4 h	2.89	13%
Monkey	1.5 h	2.36	3%
Rat	1.5 h	3.02	73%
Dog	2.0 h	0.35	100%
Monkey	2.5 h	0.13	74%

ABT-594	Rat	1.5 h	1.7	51%
	Dog	4.7 h	0.4	35%
	Monkey	1.4 h	1.7	90%
A-312046	Rat	3.0 h	1.95	80%
	Dog	1.4 h	2.89	13%
	Monkey	1.5 h	2.36	3%
A-366833	Rat	1.5 h	3.02	73%
	Dog	2.0 h	0.35	100%
	Monkey	2.5 h	0.13	74%

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Additional Characterization and Ongoing Studies

- A-312046:
 - Evaluation of viability of transdermal formulation
 - Identification of prodrug analogs
- A-366833:
 - Ames and chromosomal breakage neg.
 - CEREP binding studies -- no significant findings
 - Ongoing studies:
 - Evaluation in additional pain models
 - PK/PD studies -- plasma levels at efficacious and emetic doses
 - Dog, monkey, human hepatocyte metabolism
 - Cardiovascular evaluation
 - Two-week toxicology in rats

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Backup Status

- A-366833:
 - Broad spectrum activity, but particularly effective in persistent nociceptive pain model
 - Significantly decreased side effect liability
 - Excellent oral bioavailability across three species
 - May extend into general pain indication
- A-312046:
 - Excellent activity in neuropathic pain model
 - Pharmacokinetics may preclude development as oral drug
 - Alternative formulations may be useful as backup for AET-594 in neuropathic pain market

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ABBT 0002469

McCarthy Deposition Exhibit 38

D's Exhibit 1112

Elizabeth
Kowaluk/LAKE/PPRD/ABBO
TT
02/05/2001 10:48 AM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT,
Michael K Biemesen/LAKE/PPRD/ABBOTT@ABBOTT,
Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT,
James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Steve C
cc: Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT, Keith F
Hendricks/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K
Waleska/LAKE/PPD/ABBOTT@ABBOTT, John M
Leonard/LAKE/PPRD/ABBOTT@ABBOTT

bcc:

Subject: Re: DSG

Bruce,

Thanks for forwarding the proposed list of members for the ABT-594 Go/No Go decision analysis core team. The proposed team seems very appropriate, both in the number of members and the breadth of participation. As you note, we can involve additional members should we require input on specific issues as the analysis proceeds.

Our assistant Roz will work on scheduling a kick-off meeting for this week or early next week as individual calendars permit. Like you, I am anxious to begin work on this project ASAP.

Thanks also for summarizing the issues that arose at Friday's Leiden meeting. This will be helpful as we begin our scope and frame discussion.

Could you please send me copies of the most recent ABT-594 Development Plan, the ABT-594 Investigator's Brochure, some description of the Ph. IIb trial and any other documents you think might help me with background knowledge? I have found that reviewing such documents in advance helps me get up to speed and avoids wasting the team's meeting time to educate me.

I look forward to working with you and the rest of the team on this project.

Liz

Bruce McCarthy 02/02/2001 02:33 PM

Bruce McCarthy 02/02/2001 02:33 PM

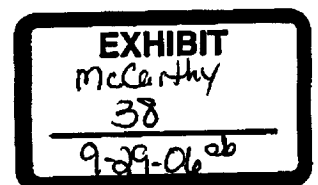
To: Elizabeth Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Biemesen/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT,
James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Steve C Kuemmerle/LAKE/PPRD/ABBOTT@ABBOTT,
Keith F Hendricks/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT,
John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT
Subject: DSG

Liz-

Per our preliminary discussions regarding the DSG process for ABT-594 Go/No Go, here is a preliminary list of core team members (see below). Please comment on the number of core team members, as you have a better perspective on how many is too many (understanding that additional project team members will be involved whenever necessary). In addition, please comment on whether the list is sufficiently comprehensive.

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ABBT328810



McCarthy Deposition Exhibit 41

P's Exhibit EW

ABT-594 / Pain Strategy Decision Analysis**Core Team Meeting – Minutes****Meeting Date:** 3/5/01**Attendees:**

Nigel Livesey	Mike Biarnesen	Liz Kowaluk
Laura Robinson	Rose Waleska	
Sandeep Dutta	Connie Faltynek	
Steve Townsend	Marleen Verlinden	
Bruce McCarthy	Mike Meyer	
Jim Sullivan	John Simons	

As a first step to establishing the frame for the analysis and structuring the decision problem, this core team meeting focused on identifying key issues specifically related to ABT-594.

The issues raised are summarized below under three broad subject headings:

- Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?
- What indications do we pursue for ABT-594, and how?
- What is the abuse liability and potential for scheduling of ABT-594?

In addition, several points were raised that are also of more general relevance to the broader subject of pain therapeutic area strategy. These are summarized at the end of this document.

Can the tolerability of ABT-594 be improved, and a therapeutic index be achieved that is consistent with regulatory and commercial viability, and how?

What is the therapeutic index that is consistent with regulatory and commercial viability? Does it differ for different pain states?

- AEs observed include nausea, emesis, dizziness and vivid dreams (at high doses)

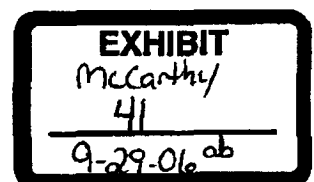
Understanding the biological basis for the PK/PD issues and the prolonged T_{max} is important for optimization of ABT-594 itself, and for backups.

The following issues are relevant to understanding whether, how and to what extent the tolerability and therapeutic index can be improved:

- Dose-response relationships for efficacy and AEs
 - may differ for different pain states, amongst AEs, and for efficacy vs. AEs
- Pharmacokinetic/pharmacodynamic relationships for efficacy and AEs
 - may differ for different pain states, amongst AEs, and for efficacy vs. AEs.
- Biological basis for efficacy and AEs?
 - C_{max} ? Rate of rise of plasma levels? Receptor occupancy? Other?

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ABBT298380



- Rate of tolerance over time for efficacy and AEs:
 - may differ for different pain states, amongst AEs and for efficacy vs. AEs.
 - must confirm that efficacy does not wane over time (weeks-months) – tolerance.
 - using titration to improve tolerability is feasible if AEs, but not efficacy tolerate.
- Mechanism of action of ABT-594:
 - preclinical pharmacology is consistent with characterization of ABT-594 as nicotinic agonist.
 - analgesia mediated by NNRs – specific site of action is uncertain
 - nausea/vomiting mediated by NNRs, mechanism of action for dizziness uncertain.
 - smokers vs. non-smokers – no effect on efficacy, but differential tolerability – has implications for dosing and labeling; potential downside for marketing – must promote understanding of receptor diversity, broad family of receptors (ABT-594 vs. nicotine).
 - gender and strain differences seen in preclinical models – implications for humans, if any, are unknown.

Titration is under investigation as an approach to improve tolerability and therapeutic index

- Feasible if AEs, but not efficacy tolerate
- Effect of first dose – rate of rise
- Titrate over days to weeks – how can titration schedule be tailored to minimize AEs?
- Patient acceptance?
- May be commercially more acceptable in neuropathic pain – efficacy/tolerability trade-off differs
- Length of titration will be important.
- Is the decline in AEs sufficient to offset the impact of titration?
- ABT-594 would be vulnerable if a new competitor has no titration

Can alternative dosage forms and routes of administration provide a means of improving tolerability and therapeutic index?

- Enteric-coated PO formulation
 - raised as possibility but not discussed in detail
- Patch
 - may be advantageous if GI AEs are a result of direct, local action of ABT-594 on GIT.
 - decreases difference between peak/trough plasma level – may have implications for efficacy and AEs.
 - permeation data suggest feasibility
 - no formulation developed as yet (would be third party – implications for royalties/COGS)
 - ABT-594 is potent analgesic – lends itself to administration by patch.
 - longer formulation development than PO – PARD.
 - trend in pain treatment is to treat pain around the clock, rather than on a PRN basis – consistent with patch formulation (e.g. Knoll – hydromorphone OROS and others).
 - would restrict ABT-594 for use in chronic conditions.
 - have limited qualitative market research, more market research needed.
 - probably commercially acceptable, although PO dosage form preferred.
 - more suited to a "niche" market.
 - pricing and COGS may be an issue.
 - has potential impact on compliance for chronic conditions
 - concern that patch formulation may lead to perception that ABT-594 is a "strong" drug that should be reserved for severe, difficult-to-manage pain.
- Depot dosage form
 - injection/implantable (weeks to months duration of action) – cf. Lupron
 - chronic pain only

- o most useful for pain that is not variable
 - o formulation must be stable at 37°C
 - o never looked at – not currently under consideration.
- Sublingual/buccal:
 - o more suitable for acute pain
 - o impact on AEs uncertain - faster rate of rise of plasma levels may precipitate AEs if this is the underlying issue, or could potentially avoid GI AEs, if they are locally mediated.
- Parenteral:
 - o potentially useful to address issues surrounding PK/PD relationship
 - o potentially "completes" product line – start on i.v. in hospital, then convert to PO.
 - o separation of efficacy and AEs may be a particular problem with rapid rate of rise of plasma levels.
 - o AEs an issue in post-op setting, where patients experience nausea/emesis – is combination with anti-emetic feasible?
- Intrathecal:
 - o may be useful in anesthesiology – would be HPD
- Intranasal:
 - o not discussed.

GI absorption and T_{max} issue

- Delayed onset of action precludes acute and general pain claims for ABT-594
- What is biological basis for the unexpectedly long T_{max} (4-5 hours after PO solid dosage form)?
- Liquid dosage forms have somewhat shorter T_{max} than solid dosage forms, but still longer than expected (and large variance).
- "White paper", summarizing current knowledge, is in preparation.
- Potential trade-offs associated with faster absorption and shorter T_{max} :
 - o increased probability of abuse liability
 - o faster onset of action,
 - o increased AEs, if AEs are related to rate of rise of plasma levels.

What indications do we pursue for ABT-594, and how?

Should our first entry be into neuropathic pain, as currently planned?

- There is no regulatory precedent for neuropathic pain – no drug has been approved for this indication, with the exception of Gabapentin in UK (but not an NCE). The most advanced compound, pregabalin, was recently withdrawn from clinical trials (carcinogenicity issues?).
- Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on the risk-benefit ratio issue. For this reason, entry to the market via a neuropathic pain indication is likely to be the preferred approach for ABT-594.
- In EU – role of the comparator is unclear (gabapentin?, Tegretol in Germany?) – placebo preferred by Abbott.
- In neuropathic pain, tolerability versus efficacy trade-off may play out differently in US versus EU. The majority of US patients are on gabapentin. In EU, patients are not switching as readily to gabapentin (may be pricing issue), majority are on TCA and carbamazepine. This may translate to a lower efficacy vs. tolerability hurdle in EU.
- What is the positioning statement for ABT-594 in neuropathic pain?

- o best neuropathic pain drug because...
- o better than gabapentin (easier to use)
- o novel mechanism of action (non-opioid, non-NSAID).

How can we broaden the use of ABT-594 beyond neuropathic pain?

- Nociceptive pain?
- General pain claim?

How do we access the nociceptive pain market with ABT-594?

- Can we study OA patients who are not responding to NSAIDs/COX-2 and progressing to opioids (i.e. second-line treatment)? Many OA patients switch between medications.
- The above is analogous to the second step of the WHO analgesia ladder – cancer patients move relatively quickly to the second step.
- For cancer pain, ABT-594 could potentially be a molecule that has opioid-like efficacy, but is not scheduled.
- Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
- In OA and low back pain, the comparison is likely to be to e.g. Vioxx – an outcome showing similar efficacy but higher AEs would not be advantageous.
- Current approach to nociceptive pain (OA) is a publication strategy - prefer indications to publication from commercial perspective.
- Barriers to entry are high (e.g. COX-2 inhibitors: 1.2 million details per year and 6000 reps.)

General pain claim not feasible for ABT-594, due to prolonged onset of action.

- Not a clear regulatory and clinical path – FDA is not necessarily accepting historical approach, wherein trials in OA/RA lead to a general pain claim. The general pain claim requires multiple models – not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
- Both FDA and EU regulatory agencies leaning towards disease-specific claims – "you get what you study".
- First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market – also more likely to get reimbursement entering into the latter market.

Is a "niche" product commercially attractive? What are the trade-offs for a "niche" compound vs. a "blockbuster" compound that is effective across a broad spectrum of pain states?

Chronic length of treatment is an issue from regulatory perspective:

- EU requires 6 months efficacy data and 1 year of safety data
- US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.

Pricing strategy:

- Gabapentin priced at 4 times the price of COX-2 inhibitors – have they priced themselves out of the market?
- Should we price like COX-2 in EU?
- Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).

Combination products:

- Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
- EU is moving away from approval of combination products.
- Not attractive as entry – co-prescribing is preferred approach.
- Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

What is the abuse liability and potential for scheduling?

The regulatory and clinical path is known.

Scheduling is commercially detrimental.

"Nicotinic PR" is a potential issue - Abbott must be proactive to counteract.

Issues of Relevance to Pain Therapeutic Area Strategy

Many of the issues listed here also appear above, but are restated here for convenience in anticipation of later discussions.

- Pain states can be categorized as nociceptive (visceral or somatic) and neuropathic, acute vs. chronic, by severity, by disease state.
- Compare different strategies for playing in entire pain market - multiple entries ("niche" products) versus a single "universally effective" compound.
- For any given compound/mechanism of action, what pain states should be pursued and in what order?
 - Both FDA and EU regulatory agencies leaning towards disease-specific claims - "you get what you study".
- Neuropathic pain
 - Efficacy/tolerability trade-off differs in neuropathic pain compared to nociceptive pain; also differs in US vs. EU for neuropathic pain - has potential ramifications for regulatory approval and commercial viability.
 - No regulatory precedent for neuropathic pain - no drug has been approved for this indication.
 - Relative unmet need in neuropathic pain, therefore regulatory agencies likely to be more open on issues of risk-benefit ratio.
 - In EU, the role of the comparator is unclear for neuropathic pain (gabapentin, Tegretol?)
- How do we access nociceptive pain - OA (first or second line), cancer pain, low back pain, other?
 - Low back pain would require long, large trials because it would be perceived that this is an entry to "general pain".
 - In OA and low back pain, the comparison is likely to be to e.g. Vioxx - an outcome showing similar efficacy but higher AEs would not be advantageous.
- Should we pursue general pain?
 - Not a clear regulatory and clinical path - FDA is not necessarily accepting historical approach, wherein trials in OA/RA lead to a general pain claim. The general pain claim requires multiple models - not currently defined, but likely to include difficult to treat conditions like chronic low back pain and fibromyalgia.
 - First market entry with a general pain claim could force the compound to a lower price point, versus first entry into the neuropathic market - also more likely to get reimbursement entering into the latter market.
- Publications vs. indications?
 - Indications preferred from commercial perspective.

- Pricing strategy
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 - Should we price like COX-2 in EU?
 - Price is considered less of an issue in US (premium pricing possible in neuropathic pain due to significant unmet need).
- Chronic length of treatment is an issue from regulatory perspective:
 - EU requires 6 months efficacy data and 1 year of safety data
 - US requires 3 months of efficacy data for OA, information to be supplied for neuropathic pain – Jim Steck/David Ross.
- Pricing strategy
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- Combination products:
 - Combinations of ABT-594 with COX-2/NSAID or opioid have been suggested in the past
 - EU is moving away from approval of combination products.
 - Not attractive as entry – co-prescribing is preferred approach.
 - Would be most appropriately considered for compounds which act synergistically with ABT-594 (not additive – co-prescribe).

McCarthy Deposition Exhibit 42

P's Exhibit EY

Abbott Portfolio Review

March 7-9, 2001

-
- Project: NNR
 - Compound: ABT-594
 - Presenter: Bruce McCarthy, MD

Revised 3/29/2005 3:44 PM dlc... Jc. ldl@mcneilab.com - 015281

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ABB297530

EXHIBIT

McCarthy

42

9-29-01 ab

ABT-594 Project Team Members

◆ Venture	Bruce McCarthy, Michael Blamesen, Marilyn Collicott, Aldona Matalonis, Alyssa O'Neill
◆ Statistics	David Morris, James Thomas, Yiming Zhang
◆ Commercial	Laura Robinson, Lisa Lux
◆ Pharmacokinetics	Walid Awni, Sandeep Dutta
◆ Discovery	Mike Meyer, Jim Sullivan
◆ PARD	Howard Cheskin, Lloyd Dias, David Stroz
◆ SPD	Jim Ciullo
◆ Metabolism	Joe Machinist, Stan Roberts
◆ Toxicology	Bill Bracken, Julia Hui
◆ Regulatory	Jim Steck, David Ross, Nigel Livesey

Revised 2/26/2008 4:19 PM All other names are confidential, 2/26/08

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ABBT297531

ABT-594 Target Indication

ABT-594 is indicated for the treatment of diabetic neuropathic pain.

Upside Claims

- ◆ Neuropathic Pain
- ◆ Post-herpetic neuralgia
- ◆ Osteoarthritis Pain
- ◆ Chronic Pain
- ◆ Cancer Pain

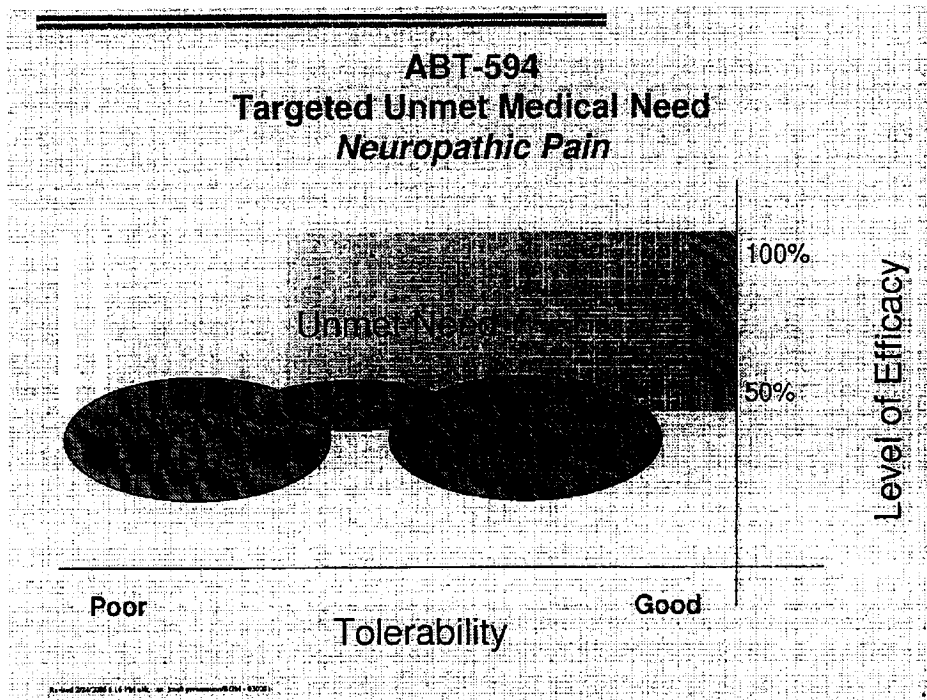
General Pain Claim

- ◆ Not viable due to 1.5 hour onset

Revised 2/24/2006 611 PM dth... and printed 2/24 - 03/201

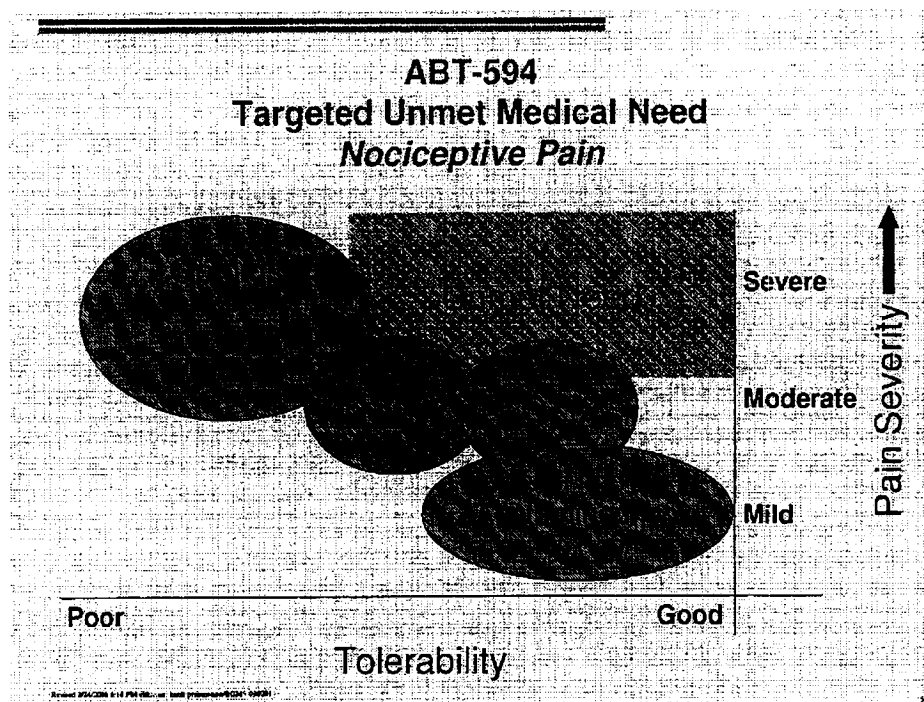
Confidential

ABBT297532



Confidential

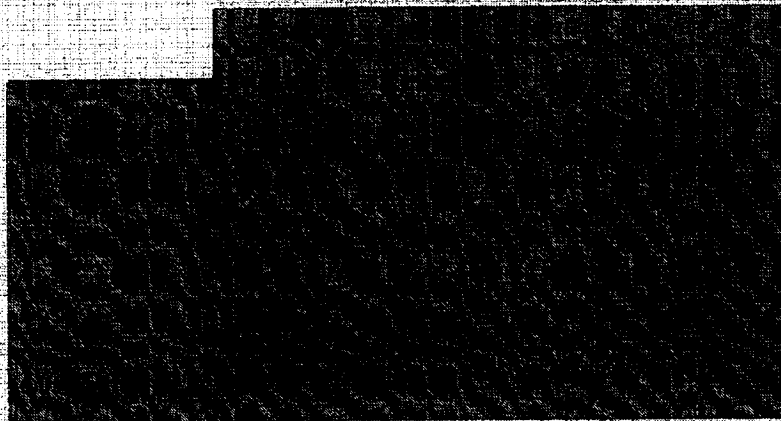
ABBT297533



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ABBT297534

ABT-594
Targeted Product Profile



Confidential

ABBT297535

ABT-594

◆ Key pre-clinical findings:

Pharmacology

- Effective across preclinical models of acute, persistent and neuropathic pain
- Retains efficacy upon repeated dosing
- Analgesia via activation of neuronal nicotinic receptors (NNRs) and not via opioid receptors
- Morphine-like side effects unexpected
 - Constipation
 - Respiratory depression
 - Sedation

PK/metabolism in animals

- No CYP interaction
- No significant metabolism

Toxicology

- No issues identified

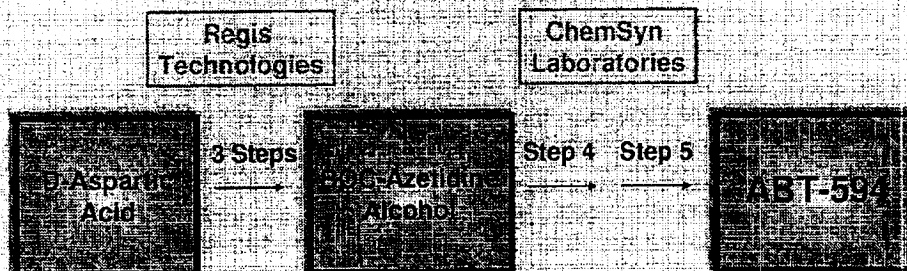
Revised 2/24/2008 8:16 PM rtk, jrt, final presentation/BDG, 030801

Confidential

ABBT297536

ABT-594

◆ Chemistry and Manufacturing: Drug Substance (Ebanicline Tosylate)



Commercial Cost Estimate: \$20,000 / Kg Tosylate Salt
 (\$40,000 / Kg Base Equivalent, approx. 3MM 300 mcg doses/kg)

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ABBT297537

ABT-594

◆ **Chemistry and Manufacturing: Drug Product**

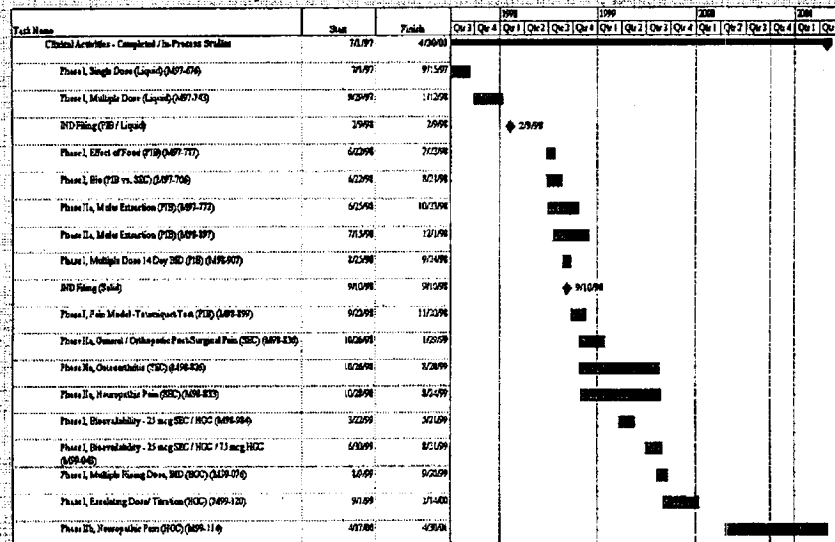
- Hard Gelatin Capsules
- Dosage strengths: 25, 75, 150 µg Base eq.
- Site: Abbott Puerto Rico
- Manufacturing process:
 - Drug is dissolved in hydro-alcoholic solution
 - Solution sprayed onto micro-porous excipient in a high-shear mixer
 - Granulation is dried, blended with excipients and encapsulated into hard gelatin capsules

Revised 3/24/2008 6:18 PM cdk...an...ball...production/BCN - 03/2008

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ABBT297538

ABT-594 Global Clinical Development Plan Completed / In-Process Studies



Revised 2/24/2005 4:15 PM ctd. - not used presentation/CD - 03/2/05

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ABBT297539

ABT-594 Global Clinical Development Plan Planned & Proposed Phase I Studies

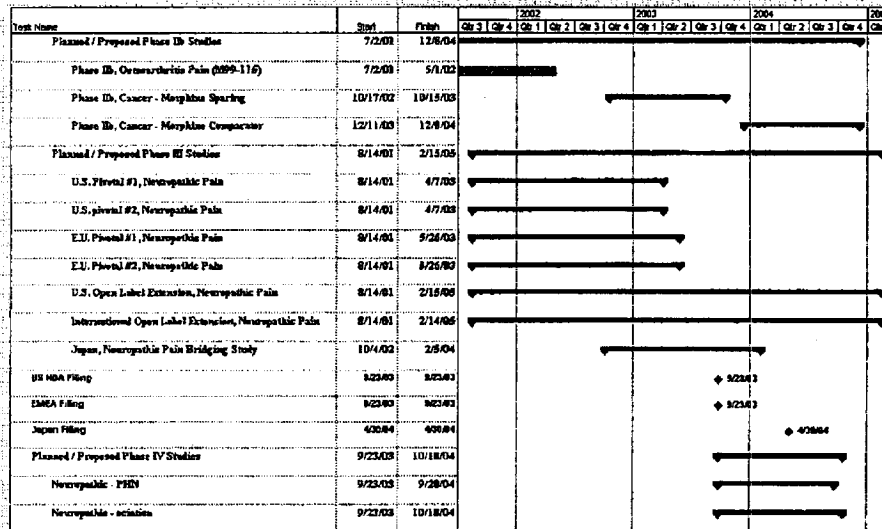
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Confidential

ABBT297540

ABT-594 Global Clinical Development Plan Planned & Proposed Phase II, III & IV Studies



Printed 2/24/2008 4:16 PM 400-000-0000-0000-0000

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ABBT297541

ABT-594 Development Budget

(\$MM)	2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
Base Program						
CMC						
- PARD	1.1	2.8	6.2	5.2	3.2	1.0
- SPD	0.1	1.0	1.0	1.0	1.0	1.0
Drug Safety	1.4	0.9	2.3	1.7	0.9	0.5
Other:	1.2	0.5	1.2			
Base Program Total	3.8	5.2	10.7	7.9	5.1	2.5
Clinical Program						
Venture Management	4.0	0.2	6.6	6.6	6.0	5.0
Data Mgmt/ Stats	0.5	0.2	5.5	7.5	4.7	2.0
Clinical Grants	1.1	0	36.8	33.7	6.0	2.0
Clinical Program Total	5.6	0.4	48.9	47.8	16.7	9.0
Annual Total Costs	9.4	5.6	59.6	55.7	21.8	11.5

Revised 8/26/2004 1:16 PM vls... (not printed) 8/26/04 1:16 PM

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ABBT297542

ABT-594

◆ Summary of Phase I findings

- Half-life ($t_{1/2}$): 8-12 hours
- Dose proportional kinetics
- AUC, C_{max} similar across formulations (solution, SEC, HGC)
- AUC, C_{max} similar with/without food
- T_{max} may vary somewhat with formulation, food
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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ABT-594

◆ Summary of Phase IIa findings

ABT-594's analgesic potential demonstrated in:

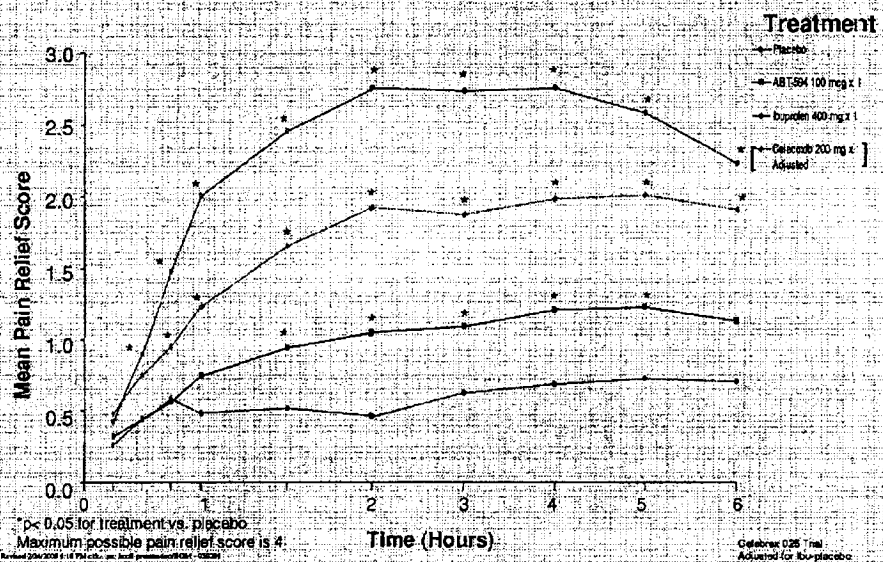
- Molar Extraction
- Neuropathic Pain
- Osteoarthritis

Well tolerated in chronic Phase IIa studies

- 75 mcg BID maximum dose

Limited additional Phase I data suggested re-evaluation of efficacy at higher doses

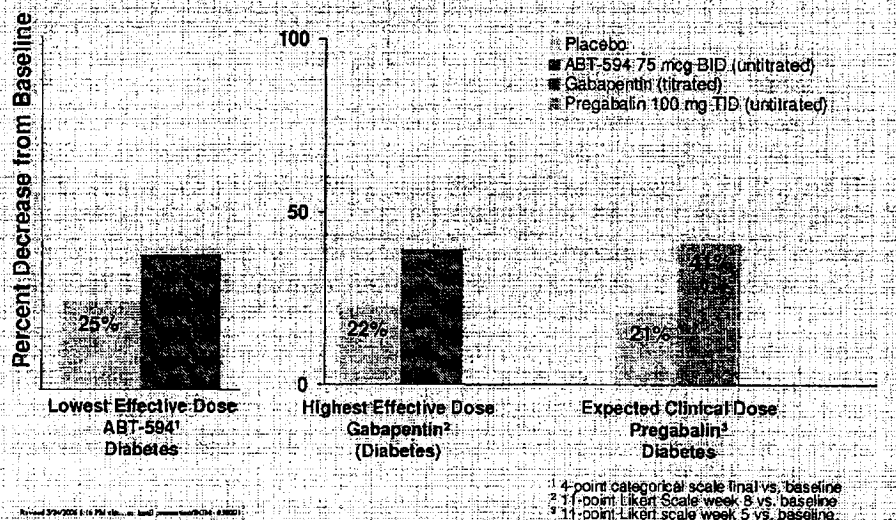
ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



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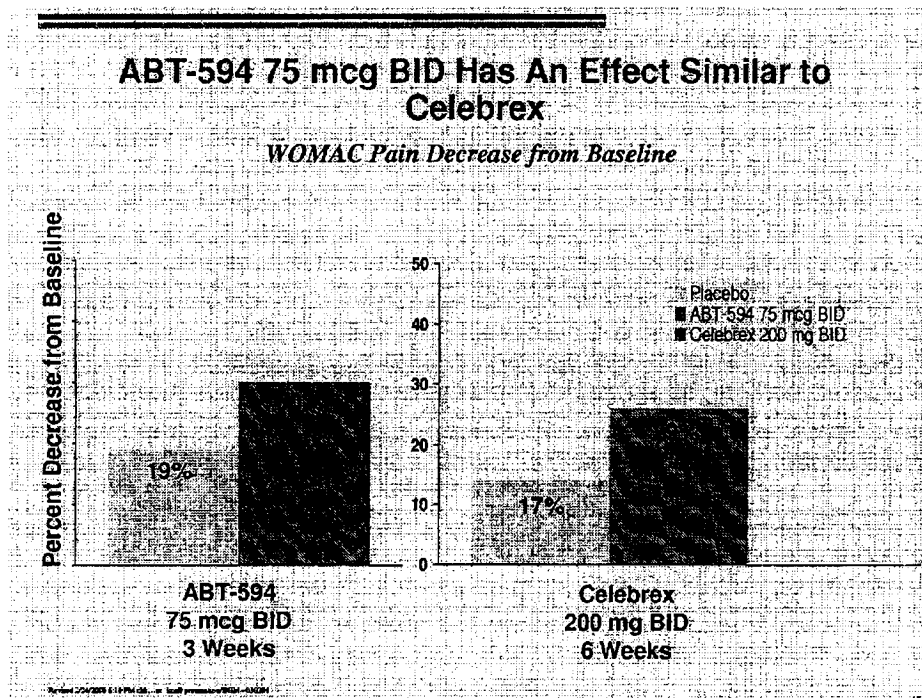
ABBT297545

**ABT-594 75 mcg BID has a
Similar Effect To Gabapentin and Pregabalin**
Average Daily Pain Score Decrease from Baseline



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ABBT297547

Adverse Event Rates for ABT-594 and Select Analgesics

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 ² 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

¹ Max. 1987 (n=29)

² M98-826 and M98-833 combined

N/A : Not Available

Revised 12/27/2005 K11 P14 sub. 100 10/27/2005/05/2005-05/2005

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ABBT297548

Adverse Event Rates for ABT-594 and Select Analgesics

Event	Ultram ¹ 50-100 mg q4-6h	OxyContin ²	OxyContin Osteoarthritis 20 mg q12h	ABT-594 ³ 75 mcg BID
Somnolence	N/A	23 %	27%	0%
Dizziness	31%	13 %	20%	7%
Nausea	34%	23 %	41%	15%
Vomiting	13%	12 %	23%	5%
Constipation	38%	23 %	32%	1%
Dry mouth	N/A	N/A	N/A	4%
Pruritis	N/A	N/A	16%	N/A

¹ Chronic non-malignant pain, up to 30 days (label)

² "Clinical trials" (label)

³ M98-826 and M98-833 combined

N/A - Not Available

Revised 3/9/2004 (U.S. Pat. & Trademark Office, 02/04)

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ABT-594

◆ Summary of Phase IIb Plans

- Neuropathic Pain

- Improved study design
- 150, 225, 300 mcg BID
- Data available 5/2001

- Osteoarthritis

- Blue plan

- Tolerability evaluation

- Rate of rise impact
- Titration

Revised 2/26/2008 8:11 AM (Rev. 10/1/2008) (Rev. 10/1/2008)

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ABBT297550

ABT-594

◆ Regulatory status:

USA, Canada

- IND 56,980, solid oral dosage form - Division of Anesthetic, Critical Care, and Addiction Drug Products (1998)
- IND 55,293, oral solution - Division of Anti-inflammatory, Analgesic, and Ophthalmic Drug Products (1998)
- Informal Teleconference with FDA, August 26, 1998 (incl. John Hyde, MD)
- End of Phase II meeting planned, October 2000

- Europe

- Phase I studies conducted, no regulatory interactions
- End of Phase II meeting planned, October 2001

- Japan

- No activity

Revised 2/24/2008 8:14 PM etc. etc. last previous/EDM - 03/08

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ABBT297551

Strategic Summary

ABT-594

◆ Key Project Strengths / Positives

Product attributes

- Orally available
- May be effective for neuropathic and nociceptive pain
- Preclinical promise: morphine-like efficacy
 - Not associated with opioid liabilities, including sedation, respiratory depression, constipation, abuse
- No currently approved drugs for diabetic neuropathic pain

Technology/Innovation

- Novel mechanism: NNR

Time to market

- Launch 4Q/2004

Business franchise strength

- Strength in hospital channel (HPD)
- Strength in neurology (neuropathic pain)
- Leverage community strength
- Leverage Knoll pain expertise

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Strategic Summary

ABT-594

◆ Potential Issues / Threats / Negatives

- Tolerability issues

- Nausea, vomiting, dizziness

- Manufacturing/cost of goods

- Potent Drug

- Efficacy

- Therapeutic index

- Clinical recruitment

- Neuropathic pain: evolving clinical research environment
- Nociceptive pain: mature clinical research environment

- Regulatory risk

- Neuropathic pain
 - Lack of precedent is threat (more difficult) and opportunity (first mover)
 - Large unmet need may facilitate

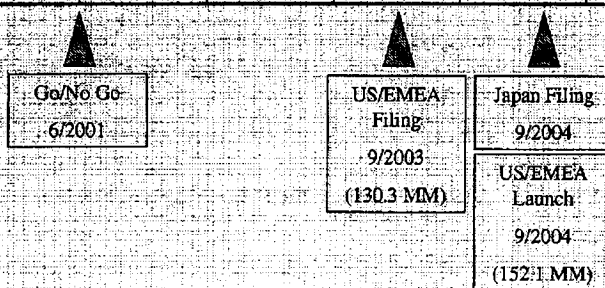
ABT-594 2004-2005 & 13 Feb 2006, last revision: 2006-01-22

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ABBT297553

ABT-594**Strategic Summary**◆ **Key Decisions****ANNUAL TOTAL COSTS (\$MM)**

2001 Plan	2001 After Go/No Go	2002	2003	2004	2005
9.4	5.6	59.6	55.7	21.8	11.5



Revised 3/24/2005 6:19 PM (MCC) - See final presentation 3/24/05

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ABBT297554

ABT-594**Strategic Summary**◆ **Proposed Action Plans****Strategic Analyses**- **Overall pain strategy**

- Abbott
- Mechanistic and therapeutic diversity and depth to achieve success

- **ABT-594 and NNRs for pain**

- Separation of adverse events and efficacy



- Oral absorption kinetics:
 - Basis of prolonged T_{max}
 - Means to improve (shorten) T_{max}
 - Implications of shortened T_{max}
- Go/No Go ABT-594
 - 6/2001

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McCarthy Deposition Exhibit 43

P's Exhibit FF

Calendar Entry

☐ Appointment ☒ Invitation ☐ Event ☐ Reminder ☐ Anniversary

Brief description:

Paul Andrews, PhD: ABT-594 Guest Speaker and Discussion
Location: Urology Work Room, AP30-3 SW Corner

Date:

03/12/2001

Time:

08:30 AM - 01:00 PM

☐ Pencil in ☐ Not for public viewing

Detailed description:

Paul Andrews, PhD
Department of Physiology
St. George's Hospital Medical School
London, UK

Paul Andrews, PhD, will be joining us for a discussion of ABT-594's tolerability issues, especially the emetic liability.

Please attend the discussion from 8:30 a.m. - 11:30 a.m. and join us for lunch from 11:30 a.m. - 12:30 p.m.

Bruce McCarthy
Marleen Verlinden

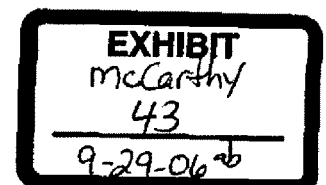
Invitations have been sent to: Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT, Mark A Osinski/LAKE/PPRD/ABBOTT@ABBOTT, Bryan F Cox/LAKE/PPRD/ABBOTT@ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep Dutta/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Michael K Biamesen/LAKE/PPRD/ABBOTT@ABBOTT, Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT

Optional invitees: Amy M Wood/LAKE/PPRD/ABBOTT@ABBOTT, Amanda J Meier/LAKE/PPRD/ABBOTT@ABBOTT, Hope R Ceaser/LAKE/PPRD/ABBOTT@ABBOTT, Mary A Metz/LAKE/PPRD/ABBOTT@ABBOTT, Nancy M Palbicke/LAKE/PPRD/ABBOTT@ABBOTT, Ericka B Moore/LAKE/PPRD/ABBOTT@ABBOTT

Chairperson: Catherine K Kacos/LAKE/PPRD/ABBOTT

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ABBT 0022006



**Paul Andrews, PhD
St. George's Hospital Medical School
London, UK**

**Meeting Agenda
Monday, 12 March 2001**

ABT-594 Discussion

Attendees: Marleen Verlinden, James Sullivan, Michael Meyer, Kennan Marsh, Walid Awni, Mark Osinski, Bryan Cox, Rick Granneman, Sandeep Dutta, David Morris, James Thomas, Michael Biarnesen, Aldona Matalonis, Bruce McCarthy

8:30 am – 9:45 am	ABT-594 Review: Preclinical Data Clinical Data	Mike Meyer Bruce McCarthy
9:45 am – 10:00 am	Break	
10:00 am – 11:00 am	Paul Andrews' Presentation Mechanisms of ABT-594 Induced Emesis	Paul Andrews
11:00 am – 12:00 pm	Discussion: Mechanism Hypothesis Generation Experiments Proposed Next Steps	
12:00 pm – 1:00 pm	Lunch	

Dexmedetomidine Discussion

Attendees: Marleen Verlinden, James Sullivan, Kennan Marsh, Bryan Cox, Mila Etropolski, Charles McLeskey, Michael Karol, Steven Buckner, Steve Collins, Victor Jorden, Bruce McCarthy

1:00 pm – 2:00 pm	Dexmedetomidine Review: Preclinical Data Clinical Data	Jim Sullivan Mila Etropolski
2:00 pm – 2:15 pm	Break	
2:15 pm – 4:00 pm	Discussion: Separation of Analgesics and CNS Effects	

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ABBT 0022007

	Dose (nmol/kg)	Retches & Vomits (avg # episodes)	Latency, min (vomitters only)	Vomiting incidence	%
ABT-594	30	—	—	0/3	0
(assayed	100	1	9.2	2/9	22
Jul-Sep '98)	300	2.7 ± 0.7	9.0 ± 2.2	5/9	56
	1000	5.7 ± 0.9	2.7 ± 0.4	3/3	100
ABT-594	10	1	12.5	1/6	17
(assayed Jul '00)	30	8	7	2/6	33
	100	10.7 ± 2.3	4.1 ± 0.4	6/6	100

Osinski/Seifert D46R
09-Mar-01

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ABBT 0022008

McCarthy Deposition Exhibit 46

P's Exhibit FK

Apr-01		ABT-594 Neuronal Nicotinic Receptor Agent																																																																			
Franchisee	Dev. Status	Generic Name	Patent Expiry	Phase II	Phase III																																																																
Neuroscience	In Progress	gabapentin	2016	Treatment of pain associated with diabetic polyneuropathy																																																																	
<p>ABT-594 is a neuronal nicotinic receptor with potential efficacy in nociceptive and neuropathic pain</p>																																																																					
U.S. Market	Unit	Value	CAGR	Unmet Need/Key Market Drivers																																																																	
	TRX	10.5MM	6%	US Significant unmet need in NP as many patients do not respond to currently available agents, many of which have unacceptable SEs. No branded marketed products currently indicated for NP (although gabapentin and/or pregabalin will likely be used by time of launch). Chronic persistent pain population is growing with aging population and also has high unmet need for non-opioid options with high efficacy.																																																																	
	Sales	35MM	22%																																																																		
Ex-US Market	Unit	Value	CAGR	Unmet Need/Key Market Drivers																																																																	
	TRX	23MM	3%	Large unmet need. Agents with greater efficacy than currently available agents with adequate tolerability for chronic usage needed. Only one agent currently indicated for neuropathic pain (gabapentin - Tegretol).																																																																	
	Sales	140MM	8%																																																																		
Development	Cost to NDA	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013																																																							
	Clinical	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0																																																							
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0																																																							
Commercial	Base Case Forecast (\$MM)																																																																				
	Financial Summary	<table border="1"> <tr> <td>Peak Sales (\$MM)</td> <td>\$359</td> <td>\$313</td> <td>\$316</td> </tr> <tr> <td>Peak Standard Margin (\$MM)</td> <td>92.3%</td> <td>83.2%</td> <td>83.2%</td> </tr> <tr> <td>Peak Tax NPV @ 12.5% (global)</td> <td>\$1.191</td> <td>\$1.191</td> <td>\$1.191</td> </tr> </table>													Peak Sales (\$MM)	\$359	\$313	\$316	Peak Standard Margin (\$MM)	92.3%	83.2%	83.2%	Peak Tax NPV @ 12.5% (global)	\$1.191	\$1.191	\$1.191																																											
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Peak Tax NPV @ 12.5% (global)	\$1.191	\$1.191	\$1.191																																																																		
Product Profile (Efficacy, Safety, Convenience)	<p>Safety/AE: Sig. N/V or dizziness in 20% of lower pts during titration; tolerable ongoing side effects at effective dose</p> <p>Efficacy: BID, titration up to 7 days</p> <p>Convenience: Greater than Neurontin</p>																																																																				
Next Go/No Go	Business Rationale	<p>ABT-594 could help to establish a strong innovative retail sector pain franchise for Abbott. Leadership position in neuronal nicotinic receptor could be generated with first drug to market. Neuropathic pain market is niche pain market with limited competition, unmet need, and limited/no promotion over past decade. High use of generic underlines dollar potential.</p>																																																																			
	Key Competitor Position to Market	<p>Neuropathic pain: Neurontin is taking strong lead in this market as increased MD awareness of efficacy coupled with use of use becomes widespread, although it lacks an indication. Pregabalin is in development for NP also and may launch with indication before 594. Chronic pain likely some spillover prescribing in this market for 594; COX-2 and opioids dominate this market, but additional options (non-MOAs) with better efficacy than NSAIDs, without the AEs and addiction potential of opioids are needed for chronic pain.</p> <p>Neuropathic pain: Gabapentin (Neurontin) on market with limited commercial success as US (total 1999 sales 180 MM for use in all indications). Gabapentin is gold standard treatment, but is not indicated for neuropathic pain, and has undesirable side effects. Pregabalin currently in Phase III. ABT-594 expected to be first to market for neuropathic pain. Chronic pain likely some spillover prescribing in this market for 594. Opioids reserved for only the most severe pain (e.g. cancer, post-op), thus large unmet need exists for non-scheduled, non-addictive agents for treatment of chronic pain.</p>																																																																			
	Development Timeline	<table border="1"> <tr> <th>Year</th> <th>2001</th> <th>2002</th> <th>2003</th> <th>2004</th> <th>2005</th> <th>2006</th> <th>2007</th> <th>2008</th> <th>2009</th> <th>2010</th> <th>2011</th> <th>2012</th> <th>2013</th> </tr> <tr> <td>Start of Phase I</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Start of Phase II</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>Start of Phase III</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>													Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Start of Phase I														Start of Phase II														Start of Phase III												
Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013																																																								
Start of Phase I																																																																					
Start of Phase II																																																																					
Start of Phase III																																																																					
Share Impact	Prob	<p>Medium</p>																																																																			
	Share Impact	<p>High</p>																																																																			
	Share Impact	<p>Medium</p>																																																																			

EXHIBIT
McCarthy
46
9-29-06 ab

Ex-US.
Jun 05
\$0.30
Comparable to premium pain meds (COX-2)
\$23
\$11
Same as US
Same as US

U.S.
Sept 04
\$337
Comparable to Neurontin/COX-2
\$26
\$28
\$40,000/kg (Base Equivalency)
Pregabalin (or other drug) launches with indication in NP - better efficacy than gabapentin, but worse side effects

Commercial Profile
Launch Date
Price per Day at Launch (per 7)
Sales force @ peak sales (\$MM)
Promo @ peak sales (\$MM)
COGS @ launch @ peak
Market/External/Other

Financial Summary
Peak Sales (\$MM)
Peak Standard Margin (\$MM)
Peak Tax NPV @ 12.5% (global)

End of Phase II (June 01)

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ABBT 0000491

April 2001

ABT-594

Monthly Highlights – Key Project Progress

- Blind Broken on April 20 for M99-114 Painful Diabetic Neuropathy Phase II b study

Next Quarter's Key Progress Markers

Key Progress Marker	Target Date
• Go / No Go target for program	06/30
•	
•	

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact _ Cost _ Time _ Profile _ X Regulatory	Strategy/Progress	Area / Responsibility	Resolution Date Planned / Actual In-Process
Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.		PARD Analytical has completed their analysis of the lab-scale batch made with the Mitsunobu chemistry change in step 4. No issues have been identified. Additional evaluation continues, looking at samples from the in-process chemistry stages to see if there are any additional targets to look for. Some degradation studies have been started, with final characterization and / or isolation to be completed.	PARD Analytical	
		The first production-scale lot of drug substance manufactured using the Mitsunobu chemistry change in step 4 has been completed. The specifications were issued 4/24 (document DTP-RD0838.) Release testing will be initiated in May, and should be completed within the month. The lot will also be put on stability in May.	SPD / PARD Analytical	Release testing complete: May QA release: TBD

2 of 6

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April 2001

ABT-594

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact — Cost — Time — Profile — X Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F ¹) was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F ¹ and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study		<p>This issue has been reviewed with PARD, SPD, Toxicology, Regulatory and Venture Management. To date, the F¹ impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made.</p> <ul style="list-style-type: none"> Progress continues on SPD's effort to synthesize 2 grams of purified F¹ material for further testing. PARD Analytical will be testing the F¹ material to confirm identity and match to impurity found in drug substance lot. When testing is successfully completed, F¹ material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics. 	<p>SPD</p> <p>PARD Analytical</p> <p>Toxicology / Exploratory Kinetics</p>	<p>June-01</p> <p>TBD</p> <p>TBD</p>
	— Cost — Time — Profile — Regulatory			

3 of 6

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April 2001

ABT-594

Key Activities

Activity	Commercial	LBE	Actual
Quantitative component analysis regarding commercial viability of various efficacy/AE profiles and associated market share tradeoffs		6/01	
Qualitative market research regarding attractiveness of transdermal patch for severe pain or neuropathic pain patients		6/01	
NNR communication strategy		12/01	
ABT 594 publication plan		12/01	
Brand name registration submission (generic name approved 11/00 - ebanolone tosylate)		12/01	

Activity	Formulation	Plan	Actual	Plan Date: 10/2000
Phase I Formulation (PIB)*		7/1997	7/1997	
Clinical Supplies (PIB) for Molar Extraction		7/1998	7/1998	
Phase II Formulation (SEC) for IND		7/1998	7/1998	
Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)		10/1998	10/1998	
Phase IIB / Formulation (HGC) for Bio Study		3/1999	3/1999	
Phase III Clinical Supplies Manufactured		9/2001	TBD	
NDA Lots (3) Completed		5/2002	TBD	
Completion of 1 Year Stability for NDA		7/2003	TBD	
Formulation Peer Review		TBD	TBD	

* Performed by IDC

Drug Substance	Activity	KG	Plan	Actual	Actual / Projected Cost/kg*	Plan Date: 6/1999
D-45L		0.3 KG	3/1997	3/1997	\$ 200,000	
CAPD		5.6 KG	3/1997	3/1997	\$ 175,000	
SICOR		14.9 KG	2/1998	2/1998	\$ 40,000	
SICOR/CAPO		2.5 KG	8/1998	8/1998	\$ 40,000	
Chemsyn Pilot Lot		1.0 KG	5/1999	5/1999	\$ 29,700	
Chemsyn Mfg. Lot		10.0 KG	10/1999	Not manufactured	\$ 29,700	
Chemsyn NDA Lot #1 (Mesylate)		4.85 KG	10/1999	2/2001 **	\$ 29,700	
Chemsyn NDA Lot #2 (Mesylate)		4.80 KG	10/1999	2/2001 **	\$ 29,700	
Chemsyn NDA Lot #3 (Mesylate)		5.45 KG	10/1999	2/2001 **	\$ 29,700	
Chemsyn Mitsunobu Lot #1		5.0 KG	04/2001			
Chemsyn Mitsunobu Lot #2		5.0 KG				
Chemsyn Mitsunobu Lot #3		5.0 KG				

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

** Bulk manufactured 1/2000, but delivery delayed due to Mesylate testing & QA release

Toxicology Activity	Planned Start	Actual Start Date	Report Completed	Plan Date: 1999
Gene Toxicology	2/1997	9/1996	8/1997	
Acute Studies	3/1997	4/1997	8/1997	
1 Month Rat/Monkey	2/1997	2/1997	11/1997	
3 Month Rat/Monkey	7/1997	6/1997	8/1998	
3 Month Mouse MTD	10/1997	6/1997	10/1998	
SEG I and SEG II	10/1997	7/1997	7/1998	
SEG III Rat (post natal development)		1/1999	Ongoing	
6 Month Rat	1/1998	3/1998	7/1999	
1 Year Monkey	6/1998	6/1998	3/2000	
Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing *	
Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing *	

* In-life phase complete, and analysis / assessment in process

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4 of 6

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April 2001

ABT-594

All Clinical Studies:

Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients		Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients	
					Target	Current						Target	Current
M99-114	II	Safety & Efficacy vs placebo in Painful Diabetic Neuropathy	04/00	04/01	320	269 Final							

5 of 6

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April 2001**ABT-594****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Status: Enrollment Complete – 269 patients randomized

Major Findings: TBD

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6 of 6

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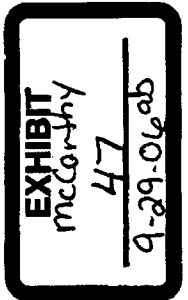
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McCarthy Deposition Exhibit 47

P's Exhibit FN

W99-114 Study Review

4/23/01



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ABBT 0001749

M99-114 Neuropathic Pain

Study Results

- Summary
- Study design
- Efficacy results
- Adverse events
- Conclusions and next steps

4/23/01 PRELIMINARY DATA

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ABBT 0001750

M99-114 Neuropathic Pain

Summary

- **Efficacy**
 - 150, 225 and 300 mcg BID are significantly better than placebo
 - All three doses may have similar efficacy
- **Safety**
 - 150 mcg BID
 - Nausea: 34%
 - Vomiting: 15%
 - Dizziness: 17%
 - Abnormal Dreams: 22%
 - Dose dependent increase in adverse events
- **Conclusion**
 - ABT-594 significantly reduces diabetic neuropathic pain

4/23/01 PRELIMINARY DATA

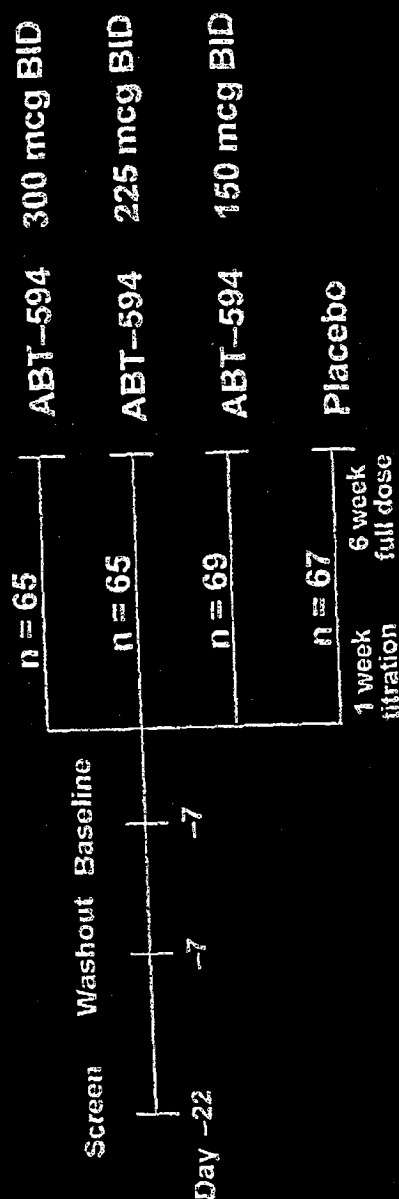
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ABBT 0001761

M99-114: Neuropathic Pain

Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power: 80% with 0.05 Type I **PRELIMINARY**
- Concomitant analgesics disallowed

4/23/01 PRELIMINARY DATA

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ABBT 0001762

M99-114: Neuropathic Pain

Outcome Measures

- **Primary**

- Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
 - Change from baseline to last 7 days on drug

- **Secondary**

- Site-based Pain Rating Scale (11-point Likert)
- Neuropathic Pain Scale
- Patient Global Impression of Change
- Clinician Global Impression of Change
- SF-36

4/23/01 PRELIMINARY DATA

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ABBT 0001753

M99-114: Neuropathic Pain

Outcome Measures

Pain Rating Scale

0	1	2	3	4	5	6	7	8	9	10
no pain										worst pain possible

Neuropathic Pain Scale (NPS)

— 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how sharp your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10
	The most sharp sensation imaginable ("like a knife")									

Subject, Clinician Impression of Change

1	Much Improved
2	Moderately Improved
3	Minimally Improved
4	No Change
5	Minimally Worse
6	Moderately Worse
7	Much Worse

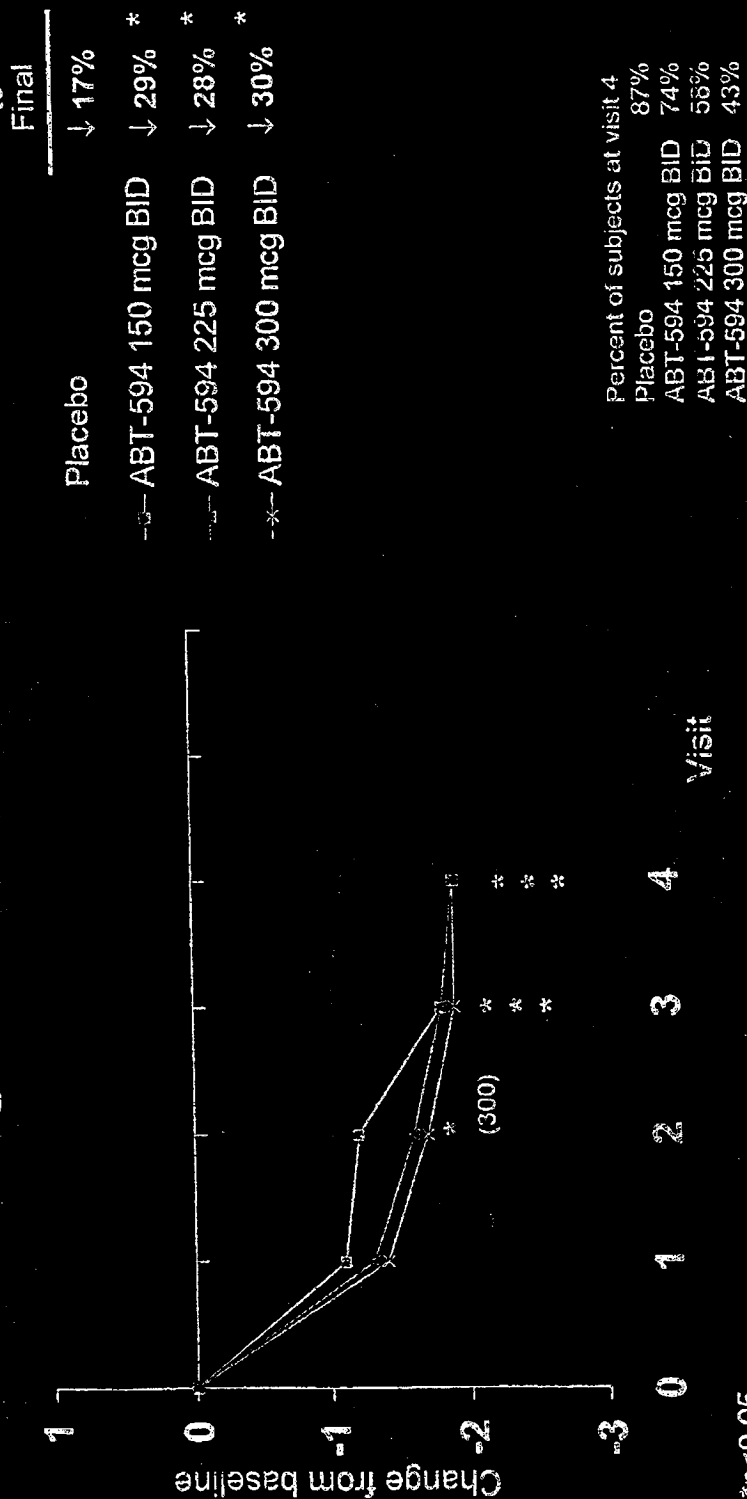
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ABBT 0001764

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Primary Efficacy Variable in the Intent to Treat Population

Pain Rating Scale-Diary (Between Visit Average) ^{Change: Baseline to Final}



*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.6

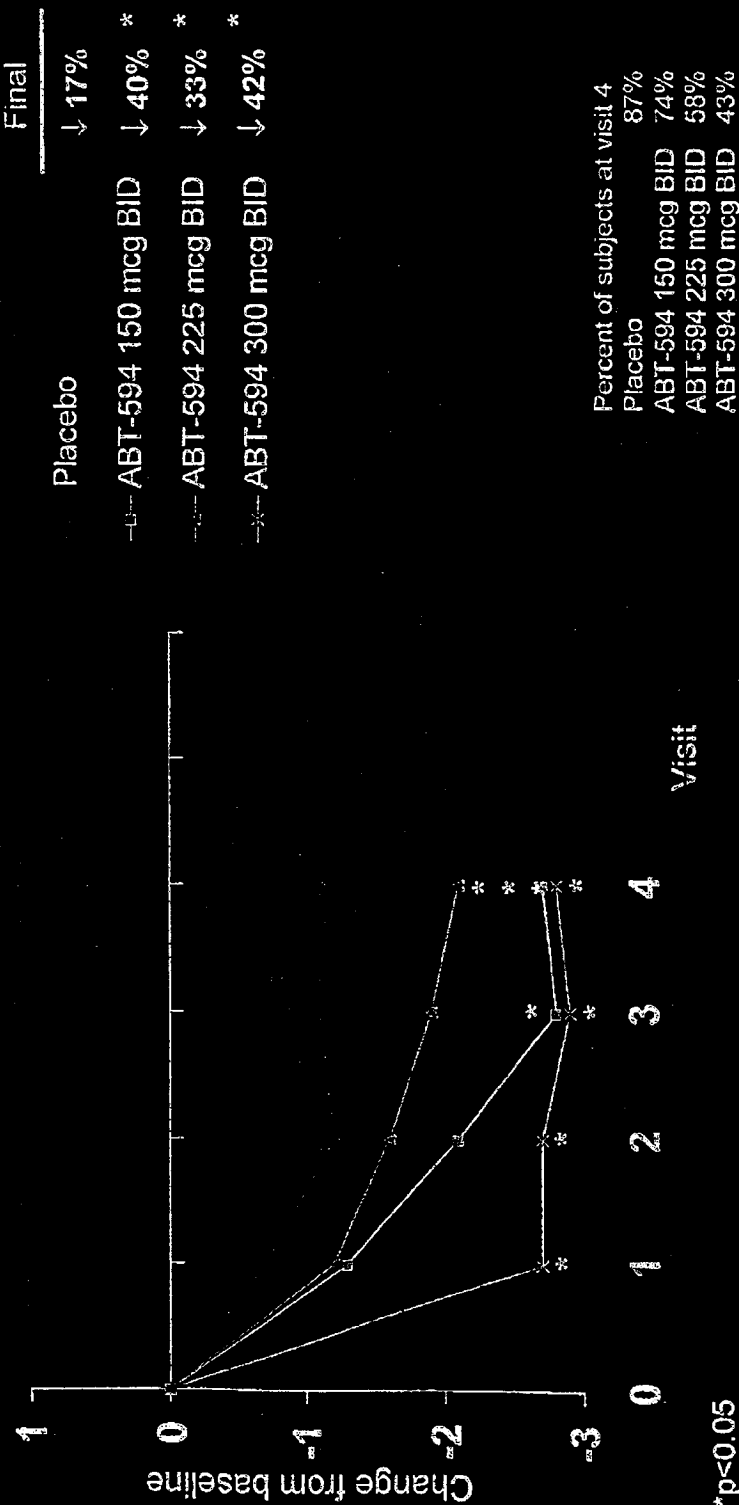
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ABBT 0001766

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale in the Intent to Treat Population

Pain Rating Scale (Site Based)



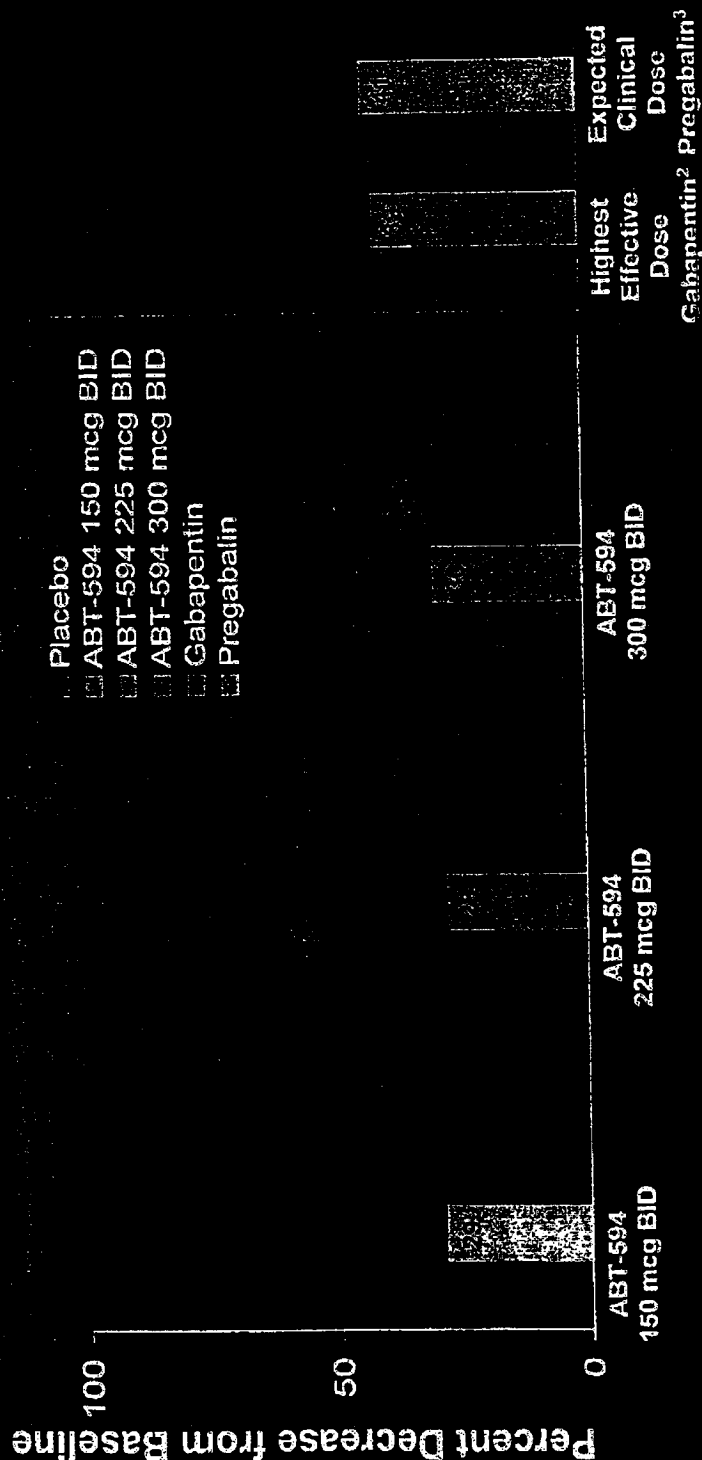
*p<0.05
Maximum possible decrease for 150 mcg BID group was 6.7
4/23/01 PRELIMINARY DATA

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ABBT 0001768

ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain as Greatly as Gabapentin or Pregabalin (ITT)

ABT-594 vs. Gabapentin and Pregabalin



1 11-point Likert scale week 7 vs. baseline
2 11-point Likert scale week 8 vs. baseline
3 11-point Likert scale week 5 vs. baseline

4/23/01 PRELIMINARY DATA

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ABBT 0001757

ABT-594 150, 225 and 300 mcg BID Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness

*Adverse Events**

Event	ABT-594		ABT-594	
	Placebo N = 65	150 mcg BID N = 65	225 mcg BID N = 69	300 mcg BID N = 67
Nausea	11 %	34 %	43 %	46 %
Abnormal Dreams	0 %	22 %	22 %	18 %
Headache	12 %	20 %	14 %	19 %
Dizziness	5 %	17 %	35 %	28 %
Vomiting	3 %	15 %	25 %	21 %
Diarrhea	3 %	11 %	12 %	6 %
Dyspepsia	3 %	8 %	12 %	7 %
Asthenia	2 %	6 %	16 %	19 %

*Occurring in $\geq 5\%$ 150 mcg BID ABT-594 treated patients and ABT-594 incidence > placebo.

4/23/01 PRELIMINARY DATA

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ABBT 0001768

McCarthy Deposition Exhibit 48

P's Exhibit FZ

Part 1

Marilyn J
Collicott /LAKE/PPRD/ABBO
TT

07/19/2001 01:59 PM

To James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT
cc

bcc

Subject 114 final report

Here ya go!



114-Final ReportMC.doc

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ABBT238577

ABBOTT LABORATORIES

Clinical Study Report No. R&D/01/171

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the
Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful
Diabetic Polyneuropathy**

ABT-594/Protocol M99-114

06 July 2001

*I have read this report and confirm that to the best of my knowledge it accurately
describes the conduct and results of the study.*

Marilyn J. Collicott
Clinical Project Manager, Analgesia Venture

Date:

David D. Morris, Ph.D.
Assistant Director, Statistics

Date:

Bruce G. McCarthy, M.D.
Medical Director, Analgesia Venture

Date:

Marleen H. Verlinden, Pharm.D., Ph.D.
Vice President, Global Pharmaceutical Research and
Development Neurology/Urology

Date:

 **Abbott Laboratories**

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ABBT238578

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

i

1.0 Title Page

ABBOTT LABORATORIES Clinical Study Report R&D/01/171

**A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and
Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy**

ABT-594/Protocol M99-114

Development Phase:	II
Investigators:	Multicenter
Date First Subject Dosed:	24 April 2000
Date Last Subject Completed Dosing:	24 February 2001
Sponsor/Signatory:	Marleen H. Verlinden, Pharm. D., Ph.D. Vice President, Global Pharmaceutical Research and Development Neurology/Urology D42U, AP30 200 Abbott Park Road Abbott Park, Illinois 60064-6145 Phone: (847) 935-4096 Fax: (847) 938-1629
Report Date:	06 July 2001

This study was conducted in compliance with Good Clinical Practice, including the
archiving of essential documents.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

ii

2.0 Synopsis

Name of Company: Abbott Laboratories	Individual Study Table Referring to Item of the	(For National Authority Use Only): N/A
Name of Finished Product: ABT-594 Hard Gelatin Capsule (HGC)	Submission: not applicable (N/A)	
Name of the Active Ingredient: Abbott-165594	Volume: N/A Page: N/A	
Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects With Painful Diabetic Polyneuropathy		
Investigator(s): Multicenter		Study Center: Multicenter
Publication (reference): not applicable		
Study Period (years):	Phase of Development: II	
Date First Subject Dosed: 24 April 2000		
Date Last Subject Completed Dosing: 24 February 2001		
Objective: The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and ≥4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.		
Methodology: This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID, or placebo for 49 days on an outpatient basis. Thirty-four sites were recruited in order to enroll approximately 320 subjects who met entry criteria for this study. Prior to any study-specific procedures at the Screening Visit, an informed consent was signed by the subject and study eligibility determined. Prior to study drug administration, subjects discontinued all analgesic medications (at least 7 days prior to the Baseline Pain Assessment Phase) and completed the 7-day Baseline Pain Assessment Phase. Following the Baseline Pain Assessment Phase, subjects who met entry criteria were randomized to a dose of study medication for 49 days (Primer and Treatment Phases). During the Primer Phase, subjects took BID doses of ABT-594 or placebo. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days. During the Treatment Phase, subjects returned to the site for Treatment Visits I, II, III and IV (Days 14, 21, 35 and 49, respectively). Subjects were to complete diary-based assessments of their diabetic polyneuropathy pain each day from the 7 days prior to study drug administration (Baseline Pain Assessment Phase) through Day 49 of study drug administration. In addition, subjects underwent site-based assessments of their neuropathic pain at the Baseline Visit and at Treatment Visits I, II, III and IV. Subjects discontinued study drug administration after Treatment Visit IV and returned to the site for the Follow-Up Visit 7-10 days later.		

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ABBT238580

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

iii

Methodology (continued):			
During the Primer and Treatment Phases, subjects were allowed to take up to 3 grams of acetaminophen per day or up to 6 grams of acetaminophen per week (but were not allowed to take acetaminophen within 24 hours prior to a Treatment Visit).			
Efficacy assessments included the Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), and Subject and Clinician Global Impression of Change. Safety assessment included physical examination, vital signs, electrocardiogram (ECG), clinical laboratory testing, and adverse event monitoring.			
No. of Subjects Planned and Enrolled:	Treatment Group	Planned	Completed/Enrolled
Planned: 320	Placebo	80	51/63
Enrolled: 266	ABT-594 150 µg BID	80	40/63
Completed: 138	ABT-594 225 µg BID	80	30/69
Premature Discontinuations: 128	ABT-594 300 µg BID	80	17/67
	TOTAL:	320	138/266
Diagnosis and Main Criteria for Inclusion:			
Adult males and females at least 18 years of age, who weighed ≤265 pounds and who were judged to be in good health based on medical history, physical examination with vital signs, laboratory profile, and 12-lead ECG, who had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit, and an average of ≥4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥4 points on the site-based Pain Rating Scale (11-point Likert Scale) at the Baseline Visit, and who met all other selection criteria were eligible for study participation.			
Test Product, Dose and Mode of Administration, Batch Number:			
<u>Test Product</u>	<u>Dose (µg)</u>	<u>Mode of Administration</u>	<u>Drug Product Lot Number:</u>
ABT-594 75 µg HGC, Formulation A-2	150, 225, and 300 BID	Oral	58-293-AR 61-312-AR
Duration of Treatment: 49 days			
Reference Therapy, Dose and Mode of Administration, Batch Number:			
<u>Test Product</u>	<u>Dose (µg)</u>	<u>Mode of Administration</u>	<u>Drug Product Lot Number</u>
Placebo for ABT-594 HGC	0	Oral	55-243-AR-01
Criteria for Evaluations:			
Efficacy:			
The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. Additionally, change from baseline to each scheduled evaluation was analyzed in a similar manner. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to Day 1 of the study.			

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

iv

Criteria for Evaluations (continued):

Efficacy:

Change from baseline to final and each evaluation was calculated for each of the following secondary efficacy variables:

- Site-Based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] physical component summary (PCS), and mental component summary (MCS).

The efficacy evaluations recorded at the Baseline Visit were used as the baseline score for efficacy evaluations assessed at the investigative site.

Pharmacokinetics:

Blood samples for ABT-594 plasma assay were to be taken from all subjects at Treatment Visits I and IV. For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max}, and C_{trough} were determined.

Safety:

Safety was assessed by medical history, physical exam, vital signs, ECG, clinical laboratory testing, and adverse event monitoring.

Statistical Methods:

For all safety and efficacy analyses, the primary comparisons were between each ABT-594 dose and placebo.

Demographic and other baseline characteristic variables were analyzed to assess the comparability of the treatment groups.

The primary and secondary efficacy variables, including change from baseline diary- and site-based pain ratings were analyzed by using appropriate parametric and nonparametric methods. The final global evaluation scores, (Subject and Clinician) were compared using Cochran-Mantel-Haenszel methodology.

Dose response for ABT-594 was explored, with and without placebo included. Other efficacy analyses were performed as appropriate.

Treatment-emergent adverse events were summarized by body system and COSTART term and compared using Fisher's exact test.

Mean change from baseline to minimum, maximum and final values were summarized for clinical laboratory, vital sign and ECG data. Additionally, clinical laboratory data identified as below or above limits were flagged in the data listings. Furthermore, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

v

Summary/Conclusions:

Efficacy Results:

ABT-594 at 150, 225, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores,

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Pharmacokinetic Results:

At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

Safety Results:

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

vi

Safety Results (continued):

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

Conclusions:

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

Date of Report: 06 July 2001

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

vii

3.0 Table of Contents for the Individual Clinical Study Report

	Page
1.0 Title Page.....	i
2.0 Synopsis.....	ii
3.0 Table of Contents for the Individual Clinical Study Report	vii
4.0 List of Abbreviations and Definitions of Terms.....	xv
5.0 Ethics	1
5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB).....	1
5.2 Ethical Conduct of the Study	1
5.3 Subject Information and Consent	2
5.4 Subject Confidentiality.....	2
6.0 Investigators and Study Administrative Structure	3
6.1 Investigative Sites.....	3
6.2 Sponsor Information.....	5
6.3 Contract Research Organization.....	5
6.4 Clinical Supply Management.....	5
6.5 Central Laboratory	6
6.6 Administrative Structure	6
7.0 Introduction	8
7.1 Analgesia Today	8
7.2 ABT-594.....	8
8.0 Study Objective.....	11
9.0 Investigational Plan	11
9.1 Overall Study Design and Plan: Description.....	11
9.2 Discussion of Study Design, Including the Choice of Control Groups	15
9.3 Selection of Study Population.....	15
9.3.1 Inclusion Criteria	15

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

viii

9.3.2	Exclusion Criteria	16
9.3.3	Removal of Subjects from Therapy or Assessment	18
9.4	Treatments	18
9.4.1	Treatments Administered	18
9.4.2	Identity of Investigational Product(s)	19
9.4.2.1	Packaging and Labeling	20
9.4.2.2	Storage and Disposition of Supplies	20
9.4.2.3	Drug Accountability	21
9.4.3	Method of Assigning Subjects to Treatment Groups	21
9.4.4	Selection of Doses in the Study	22
9.4.5	Selection and Timing of Dose for Each Subject	22
9.4.6	Blinding	22
9.4.7	Prior and Concomitant Therapy	23
9.4.8	Treatment Compliance	23
9.5	Efficacy, Pharmacokinetic and Safety Variables	24
9.5.1	Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart	24
9.5.1.1	Efficacy Measurements	26
9.5.1.2	Safety Measurements and Procedures	27
9.5.2	Appropriateness of Measurements	35
9.5.3	Efficacy Variables	35
9.5.3.1	Primary Variable	35
9.5.3.2	Secondary Variables	35
9.5.4	Drug Concentration Measurements	36
9.5.5	Pharmacokinetic Variables	37
9.5.6	Blood Samples for Genetic Polymorphism Analysis	37
9.6	Data Quality Assurance	38
9.7	Statistical Methods Planned in the Protocol and Determination of Sample Size	39
9.7.1	Statistical and Analytical Plans	39

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

ix

9.7.1.1	Data Sets Analyzed.....	39
9.7.1.2	Demographic and Other Baseline Characteristics	40
9.7.1.3	Efficacy Analyses.....	40
9.7.1.4	Pharmacokinetic Analyses.....	43
9.7.1.5	Safety Analyses.....	44
9.7.2	Determination of Sample Size	45
9.8	Changes in the Conduct of the Study or Planned Analyses	46
9.8.1	Protocol Changes.....	46
9.8.2	Statistical Changes.....	46
10.0	Study Subjects	47
10.1	Disposition of Subjects	47
10.2	Protocol Deviations	51
11.0	Efficacy and Pharmacokinetic Evaluation.....	52
11.1	Data Sets Analyzed.....	52
11.2	Demographic and Other Baseline Characteristics.....	54
11.2.1	Demographics.....	55
11.2.2	Other Baseline Characteristics.....	56
11.2.3	Concurrent Medication Use	57
11.3	Measurements of Treatment Compliance.....	57
11.4	Efficacy Evaluations and Tabulations of Individual Subject Data	57
11.4.1	Efficacy Analyses.....	58
11.4.1.1	Primary Efficacy Variable.....	59
11.4.1.2	Secondary Efficacy Variables.....	60
11.4.1.3	Other Efficacy Variables	67
11.4.2	Statistical and Analytical Issues.....	68
11.4.2.1	Adjustments for Covariates.....	68
11.4.2.2	Handling of Dropouts or Missing Data.....	68
11.4.2.3	Interim Analyses and Data Monitoring	68

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

x

11.4.2.4	Multicenter Studies	69
11.4.2.5	Multiple Comparisons/Multiplicity	69
11.4.2.6	Use of an "Efficacy Subset" of Subjects	69
11.4.2.7	Active-Control Studies Intended to Show Equivalence	69
11.4.2.8	Examination of Subgroups	69
11.4.3	Tabulation of Individual Response Data	70
11.4.4	Drug Dose, Drug Concentration, and Relationship to Response	70
11.4.5	Drug-Drug and Drug-Disease Interactions	70
11.4.6	By-Subject Displays	70
11.4.7	Efficacy Conclusions	71
11.5	Pharmacokinetic Variables	71
12.0	Safety Evaluation	72
12.1	Extent of Exposure	72
12.2	Adverse Events	73
12.2.1	Brief Summary of Adverse Events	73
12.2.2	Display of Adverse Events	74
12.2.3	Analysis of Adverse Events	76
12.2.4	Listing of Adverse Events by Subject	77
12.3	Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	77
12.3.1	Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	78
12.3.1.1	Deaths	78
12.3.1.2	Other Serious Adverse Events	78
12.3.1.3	Other Significant Adverse Events	80
12.3.2	Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	83
12.3.3	Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	83

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xi

12.4	Clinical Laboratory Evaluation.....	84
12.4.1	Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value	84
12.4.2	Evaluation of Each Laboratory Parameter	85
12.4.2.1	Laboratory Values Over Time	85
12.4.2.2	Individual Subject Changes	91
12.4.2.3	Individual Clinically Significant Abnormalities	91
12.5	Vital Signs, Physical Findings, and Other Observations Related to Safety.....	95
12.5.1	Listing of Individual Measurements by Subject and Each Abnormal Value.....	95
12.5.2	Findings on Physical Examination	95
12.5.3	Vital Signs Evaluation.....	95
12.5.3.1	Vital Signs Values Over Time	95
12.5.3.2	Individual Subject Changes	96
12.5.4	Electrocardiogram Evaluation.....	97
12.5.4.1	ECG Values Over Time	97
12.5.4.2	Individual Clinically Significant Abnormalities	97
12.5.4.3	Individual Clinically Significant Abnormalities	97
12.6	Safety Conclusions	98
13.0	Discussion and Overall Conclusions.....	100
14.0	Tables, Figures, and Graphs Referred to but not Included in the Text	102
15.0	Reference List	
16.0	Appendices	
16.1	Study Information	
16.2	Subject Data Listings	
16.3	Case Report Forms	
16.4	Individual Subject Data Listings	

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

xii

3.0 Table of Contents for the Individual Clinical Study Report (continued)

	Page
List of In-Text Tables	
Table 6.1a Distribution of Subjects by Investigator and Treatment Group	4
Table 9.4a ABT-594 Dose Escalation	19
Table 9.4b Number and Type of Capsules by Treatment Group	19
Table 9.4c Identity of Investigational Products	20
Table 9.5a Study Procedures Flow Chart	25
Table 9.5b Clinical Laboratory Tests	30
Table 10.1a Disposition of Subjects	49
Table 11.1a Disposition of Subjects by Dataset	53
Table 11.2a Demographic Characteristics (All Treated Subjects)	55
Table 11.2b Other Baseline Characteristics (Intent-to-Treat Dataset)	56
Table 11.4a Summary of the Analysis of Mean Change From Baseline ^a to Final ^b for the Average Diary-Based Pain Rating Scale ^c Scores Using LOCF Method (Intent-to-Treat Dataset)	60
Table 11.4b Change from Baseline to Final for Secondary Efficacy Variables ^a Using LOCF Method (Intent-to-Treat Dataset)	62
Table 11.4c Change from Baseline to Final for Subject and Clinician Global Impression of Change ^a Using LOCF Method (Intent-to-Treat Dataset)	63

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xiii

Table 11.4d	Summary of the Analysis of Mean Change From Baseline ^a to Each Week for the Average Diary-Based Pain Rating Scale ^b Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)	65
Table 11.4e	Proportion of Subjects Responding ^a to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores ^b Using LOCF Method (Intent-to-Treat Dataset)	67
Table 12.1a	Extent of Exposure	72
Table 12.2a	Summary of Most Frequently Reported ^a Treatment-Emergent Adverse Events By Relationship to Study Drug	75
Table 12.3a	Subjects Reporting Serious Adverse Events During the Study	79
Table 12.3b	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)	81
Table 12.3b	Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)	82
Table 12.4a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters	86
Table 12.4a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)	87
Table 12.4b	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters	89

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xiv

Table 12.4b	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued).....	90
Table 12.4c	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters	91
Table 12.4d	Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	92
Table 12.4e	Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	93
Table 12.4f	Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	94
Table 12.5a	Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters.....	96
Table 12.5b	Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects).....	98

List of In-Text Figures

Figure 6.6a	Administrative Structure.....	7
Figure 9.1a	Study Schematic	12
Figure 10.1a	Disposition of Subjects	50

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

xv

4.0 List of Abbreviations and Definitions of Terms

List of Abbreviations

ABT-594	[(R)-5-(2-azetidinylmethoxy)-2-chloropyridine] or Abbott-165594
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
CMH	Cochran-Mantel-Haenszel
DNA	Deoxyribonucleic acid
EDTA	Edetic acid
HGC	Hard gelatin capsule
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
MCS	Mental component summary
nAChR	Nicotinic acetylcholine receptor
NCR	No carbon required
NPRO	New Product Research Order
OC	Observed cases
PCS	Physical component summary
SEC	Soft elastic capsule
SF-36™	Short Form-36 Health Status Survey
SSRIs	Serotonin-specific reuptake inhibitors
TENS	Transcutaneous electrical nerve stimulation

Terms

Hemoglobin A _{1c}	Glycosolated hemoglobin
NOMAD®	A data management system

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

1

5.0 Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that approval be obtained from a research committee (e.g., Institutional Review Board [IRB], Independent Ethics Committee [IEC]), prior to participation of human subjects in research. The investigator obtained a duly constituted IRB/IEC review and approval of the protocol, informed consent form and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects). Abbott Laboratories received documentation of the study approval, the signed signature page from the study protocol, a signed Abbott Financial Disclosure form, subject informed consent document, a current investigator curriculum vitae, a signed Food and Drug Administration (FDA) Form 1572 or equivalent document, a list of members of the IRB committee and their qualifications and affiliations prior to authorizing the shipment of study drug supplies to the site. Any amendments to the protocol required IRB approval prior to implementation of any changes made to the study design. No annual IRB re-approvals were required since the study was completed within 1 year. A complete list of documents required prior to initiation of the study is located in the study protocol (Appendix 16.1.1). Information regarding the IRB is presented in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the protocol, GCP, FDA regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki (1996 Version) and all applicable local regulations. The investigator ensured that the study was conducted in accordance with prevailing local laws and customs or complied with the provisions as stated in the FDA guidelines. Responsibilities of the Investigator are specified in the study protocol (Appendix 16.1.1).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

2

5.3 Subject Information and Consent

The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Elements of the Informed Consent are specified in the study protocol (Appendix 16.1.1). A sample copy of the informed consent is presented in Appendix 16.1.3.

5.4 Subject Confidentiality

All reports and communications relating to subjects in the study identified each subject only by the subject's initials (first, middle, last) and by the subject's randomization number. Case report forms (CRF) were used to transmit the information collected in the performance of this study to Abbott Laboratories and to governmental agencies. Portions of the subject's medical records pertinent to the study were reviewed by Abbott Laboratories personnel or their designee and possibly by government personnel to ensure adequate source documentation, accuracy, and completeness of the CRFs.

The site collected information on the subject per International Conference on Harmonization (ICH) requirements, including subject name, home address, phone number, and birthdate. In addition, the name, address, and phone number of another person who could be contacted in an emergency was also recorded. This information was treated with strict adherence to professional standards of confidentiality and was filed at the site.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

3

Neither the subject, the subject's physician, nor the investigator were informed of the subject's pharmacogenetic results, if obtained. If performed, the pharmacogenetic results from individual subjects were kept confidential and were not given to anyone not directly involved with this research study. The deoxyribonucleic acid (DNA) samples are being stored by Abbott Laboratories in a secure storage space with adequate measures to protect confidentiality. The DNA samples are being kept by Abbott Laboratories until destroyed by Abbott when this research is completed or the required sample retention time has been satisfied.

6.0 Investigators and Study Administrative Structure

6.1 Investigative Sites

Thirty-four investigators in the United States were recruited to perform the study and received study drug supplies. Twenty-nine of these investigators randomized at least 1 subject. The study was conducted from 24 April 2000 to 24 February 2001. Complete names, addresses, and affiliations of the principal investigators are included in Appendix 16.1.4. The distribution of all enrolled subjects for each investigator is presented by randomized treatment group in Table 6.1a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

4

Table 6.1a Distribution of Subjects by Investigator and Treatment Group

Investigator	Total Subjects Enrolled	Treatment Group			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Backonja	3	1	1	0	1
Baumel	15	4	4	4	3
Biton	7	1	2	2	2
Bromberg	13	3	3	4	3
DeBold	12	3	3	3	3
Drucker	6	1	1	2	2
Eisner	6	1	1	2	2
Forde	2	0	0	1	1
Fried	9	2	2	3	2
Gibson	18	5	5	4	4
Gleeson	7	2	2	2	1
Haag	6	1	1	2	2
Hewitt	8	2	2	1	3
Holmlund	5	1	1	1	2
Kafka	7	2	1	2	2
Kipnes	15	4	3	4	4
Kirby	10	3	2	3	2
Kluge	9	2	2	2	3
McGill	8	2	2	2	2
Rowbotham	4	1	1	1	1
Shaibani	17	4	5	4	4
Simmons	6	1	2	2	1
Singer	15	4	4	4	3
Sivakumar	9	2	3	2	2
Steel	8	2	2	2	2
Storey	13	3	4	3	3
Suri	3	1	1	0	1
Vinik	6	2	1	2	1
Weinstein	19	5	4	5	5
Total	266	65	65	69	67

Cross Reference: Table 14.1_1.1

Highly Confidential

ABBT238597

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

5

6.2 Sponsor Information

The sponsor coordinated the activities for initiating this clinical study. The protocol, CRFs and sample informed consent form were generated by Abbott Laboratories. The database for this study was created using NOMAD®, a data management system. Designated statisticians at Abbott Laboratories were responsible for the statistical analysis of the data. A copy of the signature page for the study summary with the signature of the Abbott Laboratories' responsible Medical Officer is included in Appendix 16.1.5.

6.3 Contract Research Organization

Abbott Laboratories delegated prestudy (if necessary) and initiation visits, site monitoring, and post-study site visits to the following Contract Research Organization (CRO) for the conduct of this clinical study:

Research Solutions Inc.
3200 Chapel Hill Nelson-Highway, Suite 100
P.O. Box 14561
Research Triangle Park, NC 27709
1-800-807-7462

The sponsor and CRO maintained contact in order to manage adequately the progress of the study. The CRO coordinated and performed all site visits and prepared trip reports, using the Abbott Laboratories format, for each visit performed. These reports detailed the activities conducted at all investigative sites and included all relevant observations. All trip reports were forwarded to Abbott Laboratories in a timely manner to ensure appropriate site management, adhering to Abbott Laboratories Standard Operating Procedures.

6.4 Clinical Supply Management

Clinical supplies were prepared by Abbott Laboratories (Investigational Drug Services, D-492) for the study and sent to all investigational sites. Abbott Laboratories authorized the release of clinical supplies once the appropriate essential documents were received from the respective site and upon approval by Abbott Laboratories Regulatory Affairs.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

6

All subjects were centrally randomized by site and assigned to a treatment group (using the randomization supplied by Abbott Laboratories) using an Interactive Voice Response System (IVRS). The IVRS was contracted from:

ClinPhone Inc.
29 Emmons Drive, C40
Princeton, NJ 08540

Blinded study medication for each randomized subject (using the randomization supplied by Abbott Laboratories) was also assigned using the IVRS. Each site kept an accurate inventory of the clinical supplies, including drug shipping and receiving documents, dispensing/accountability records, and records for return of clinical supplies to Abbott Laboratories. Clinical Research Associates (CRAs) from the CRO checked drug accountability records regularly.

6.5 Central Laboratory

This study utilized 1 central laboratory. All protocol-specified clinical laboratory tests were performed by the following central laboratory:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214
(800) 462-8887

The ABT-594 plasma assays were performed under the supervision of Raymond Wieboldt, Ph.D. of the Drug Analysis Department of Abbott Laboratories, Abbott Park, IL.

6.6 Administrative Structure

The administrative structure for this study is depicted in Figure 6.6a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

7

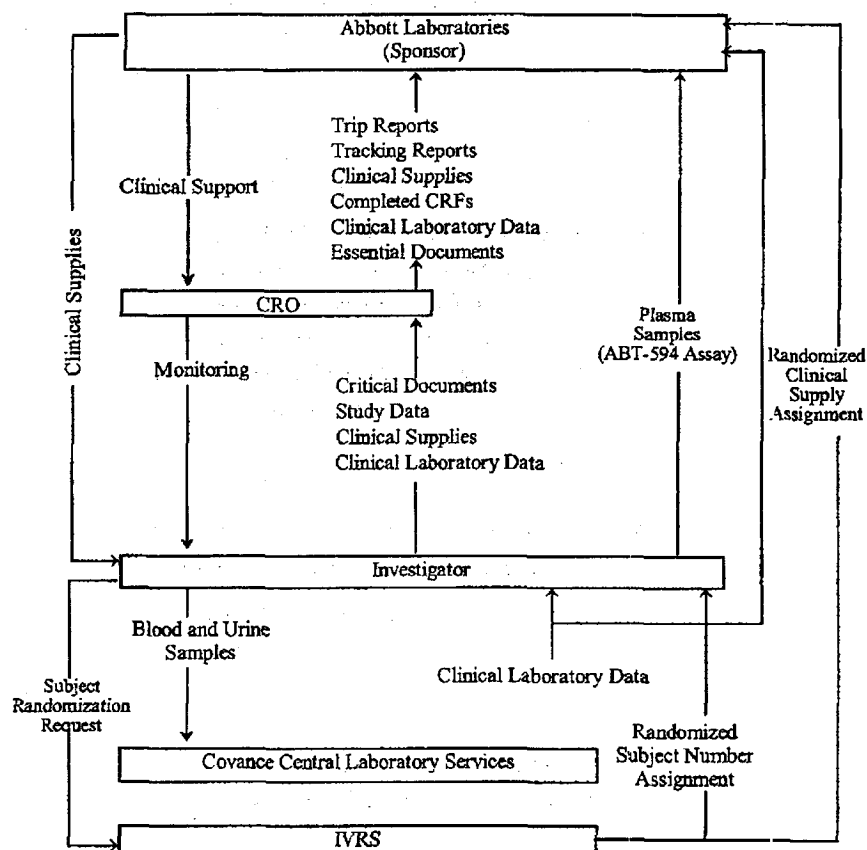


Figure 6.6a Administrative Structure

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

8

7.0 Introduction

7.1 Analgesia Today

Pain is one of the most common reasons people consult a physician, representing an extraordinary societal burden. The cost of chronic pain has been estimated to range in the tens of billions of dollars annually.¹

Currently there are 4 major groups of therapeutics for pain relief: 1) nonsteroidal anti-inflammatory drugs (NSAIDs/COX-2 inhibitors), 2) opioids, 3) adjuvant analgesics (e.g., tricyclic antidepressants), and 4) centrally acting non-narcotic analgesics (e.g., acetaminophen, tramadol). NSAIDs are most often used to treat mild to moderate pain associated with inflammation, but are ineffective in treating some types of nociceptive and neuropathic pain. Risks associated with NSAIDs include gastrointestinal bleeding and hepatic toxicity. COX-2 inhibitors may improve on this gastrointestinal profile, but other adverse events may become evident. Opioids are used for moderate to severe pain. Clinically significant physical dependence and tolerance to analgesia may occur in subjects receiving opioids regularly. In addition, constipation is a significant side effect. Adjuvant analgesics are commonly used for neuropathic pain. Unlike the other groups, the majority of adjuvant analgesics have a delayed onset of analgesia because of their mechanism of action and the requirement for dose titration. Therefore, a class of compounds with a broad spectrum clinical activity, efficacy in moderate and severe pain, and without the liabilities of opioids, NSAIDs and other currently available analgesics would represent an important advance in pain relief.

7.2 ABT-594

Interest in the potential analgesic activity of compounds acting at neuronal nicotinic acetylcholine receptors (nAChRs) has been enhanced recently by the discovery that (±)-epibatidine, a potent nAChR agonist, is greater than 100-fold more potent than morphine in rodent models of antinociception.² The antinociceptive effects of (±)-epibatidine are blocked by the nAChR antagonist mecamylamine, but not by opioid receptor blockade. Thus, (±)-epibatidine appears to be a potent antinociceptive agent that acts via activation of neuronal nAChRs and not through opioid receptors. Unfortunately, (±)-epibatidine is

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

9

quite potent at all subtypes of the nAChR (neuronal, ganglionic, and neuromuscular junction) and is quite toxic at antinociceptive doses.³ Because of nAChR diversity, however, it is possible that nAChR ligands with greater receptor subtype selectivity might have therapeutic utility at doses below those associated with side effects.

ABT-594 [(R)-5-(2-azetidylmethoxy)-2-chloropyridine], is a non-opioid, non-NSAID analgesic. It is a novel neuronal nAChR ligand that is 30- to 100-fold more potent and equally efficacious to morphine in treating moderate to severe pain in several well-characterized animal models of nociception. ABT-594 modulates pain transmission by interacting with nAChRs, and not opioid receptors, at key regulatory sites along the pain pathway. It has both peripheral and central antinociceptive effects in preclinical models of acute thermal, persistent chemical, and neuropathic pain states.

To date, only systemic treatment with opioids like morphine has been reported to have this broad spectrum of analgesic activity. Like the opioids, ABT-594 can selectively modulate pain transmission by inhibiting substance P release from C-fibers at the level of the dorsal horn, and by activating the brainstem centers that provide descending inhibitory pathways known to gate painful stimuli. In contrast to morphine, repeated treatment with ABT-594 in pre-clinical studies did not produce withdrawal effects at termination of treatment, suggesting an absence of physical dependence liabilities.

In pre-clinical studies, ABT-594 distributes rapidly to the brain following systemic administration and, like morphine, may work at multiple levels in the central and peripheral nervous systems to modulate pain perception. Compounds like ABT-594 that can selectively modulate neuronal nAChR function and possess broad-based antinociceptive activity may provide a novel therapeutic approach to pain management that avoids the liabilities typically associated with opioid analgesics.

Initial clinical trials in humans were conducted using oral solution formulations. Subsequently, a soft elastic capsule (SEC) formulation and, later, a hard gelatin capsule (HGC) formulation were developed and used in clinical trials.

Phase I clinical trials of the oral solution formulations suggested that 150 µg/day would be the maximally tolerated dose. Subsequent experience in Phase I and II trials with the solid

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

10

formulations (SEC and HGC), however, has suggested that higher doses would be tolerated. Preliminary data from Study M99-076 demonstrated that the ABT-594 HGC formulation was generally well tolerated at fixed (untitrated) doses up through 300 µg BID for 14 days. Study M99-120⁴ included titrated doses up through 450 µg BID for 5 days. Results from Study M99-120 suggested that a short period of dose escalation at the initiation of therapy improved tolerability. Throughout the Phase I studies of ABT-594, subjects generally tolerated ABT-594 better when dosing followed a meal and after 3-4 days of repeated dosing (the period in which most adverse events occur).

To date, Phase II trials have included efficacy and safety studies of ABT-594 in molar extraction, osteoarthritis and neuropathic pain. Based upon preliminary data from Study M97-772, a study of molar extraction pain, 100 µg ABT-594 (single-dose oral solution) appeared to be a minimally efficacious dose in acute pain.

A study of ABT-594 in osteoarthritis (M98-826)⁵ evaluated the ABT-594 SEC formulation at doses of 25, 50 and 75 µg BID for 3 weeks, and a study of ABT-594 in neuropathic pain (M98-833),⁶ evaluated the same formulation at doses of 25 and 75 µg BID for 3 weeks. Both studies suggested a trend towards analgesic effect at 75 µg BID. In addition, 75 µg BID was generally well tolerated. The most common adverse events (≥5%) for subjects receiving 75 µg BID ABT-594 in the osteoarthritis and neuropathic pain studies (combined) were nausea (15%), headache (13%), dizziness (7%), insomnia (6%) and vomiting (5%). ABT-594 appeared to be tolerated better after the first week of therapy (an effect not related to premature discontinuations).

Data from the Phase I and II studies completed to date suggest that ABT-594 should be generally well tolerated at doses higher than previously studied in Phase II trials (higher than 75 µg BID). In addition, data from the Phase II trials suggest that, because a trend toward analgesic efficacy was seen at 75 µg BID, a study of higher doses may demonstrate greater analgesic efficacy. The current study, therefore, was performed to test this hypothesis.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

11

8.0 Study Objective

The objective of this study was to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who had painful distal symmetric diabetic polyneuropathy, had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days), and had ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.0 Investigational Plan

9.1 Overall Study Design and Plan: Description

This was a Phase II, randomized, double-blind, placebo-controlled, multicenter study to examine the safety and analgesic efficacy of ABT-594 in subjects who had painful diabetic polyneuropathy. Approximately 320 subjects were to be assigned randomly in an equal ratio to receive 1 of 4 treatments: ABT-594 150 µg, 225 µg, 300 µg BID or placebo for 49 days on an outpatient basis. Approximately 30 sites were to be recruited in order to enroll approximately 320 subjects who met entry criteria.

The study was divided into 5 phases: Screening Phase (Day -22 to Day -8), Baseline Pain Assessment Phase (Day -7 to Day -1), Primer Phase (Day 1 to Day 7), Treatment Phase (Day 8 to Day 49) and Post-Treatment Phase (Day 50 to Day 59). Day 1 was the first day of study drug administration. Subjects were allowed a window of ± 3 days for each study visit. A schematic of the study design is presented in Figure 9.1a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

12

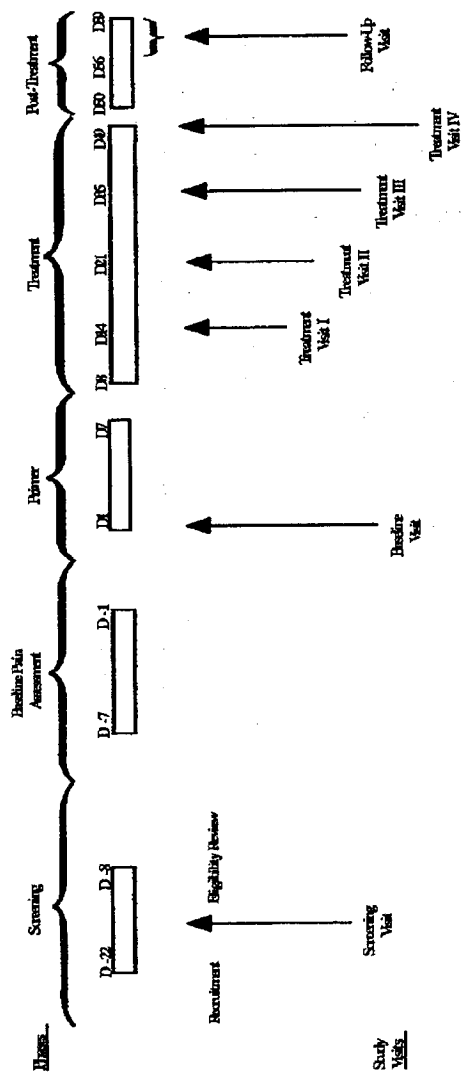


Figure 9.1a Study Schematic

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ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

13

Subjects reviewed and signed the informed consent prior to the conduct of any study specific procedures. Subjects were screened for eligibility by medical history, physical examination, vital sign measurements, and clinical laboratory tests. Those subjects taking tricyclic antidepressants, serotonin-specific reuptake inhibitors (SSRIs), antiepileptic drugs, or other analgesics for the treatment of their pain were to have discontinued these drugs at least 7 days prior to the Baseline Pain Assessment Phase. During the Baseline Pain Assessment Phase, at approximately 11 AM each morning, subjects were to complete the diary-based Pain Rating Scale (11-Point Likert Scale) of their diabetic polyneuropathy pain intensity.

On the day after the Baseline Pain Assessment Phase, subjects returned to the site for their Baseline Visit (Day 1). At this visit, diaries were collected and reviewed. In addition, subjects were to complete the site-based Pain Rating Scale (11-Point Likert Scale). Subjects who met all entry criteria, including an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Visit, completed the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute). Subjects underwent an interim medical history, physical examination, vital sign measurements, electrocardiogram (ECG), and clinical laboratory tests.

Subjects who met all entry criteria at the Baseline Visit were randomly assigned in an equal ratio into 1 of 4 treatment groups: ABT-594 150 μ g, 225 μ g, 300 μ g BID, or placebo. Subjects started study drug at the evening dose on Day 1. During the Primer Phase, subjects received a fixed dose escalation of ABT-594 or placebo (Section 9.4.1). The dose was increased every 2 days in 75- μ g BID increments until subjects were taking their assigned treatment dose (150 μ g, 225 μ g, or 300 μ g BID). Following the Primer Phase, subjects entered the Treatment Phase (Day 8) and continued their treatment for a total of 49 days.

Throughout the course of the study, subjects were not permitted to take concomitant analgesics, except for limited doses of acetaminophen (3 grams daily maximum or 6 grams maximum during the Baseline Pain Assessment Phase, and 6 grams maximum per week for

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

14

each of the 7 weeks of the Primer and Treatment Phases; Section 9.4.7). Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of Treatment Visits I, II, III and IV.

Subjects were to complete the diary-based Pain Rating Scale each morning, 3 hours after taking their morning dose of study drug (approximately 11 AM). They returned to the site for study procedures on Day 14 (Treatment Visit I), Day 21 (Treatment Visit II) and Day 35 (Treatment Visit III) and Day 49 (Treatment Visit IV). Procedures during Treatment Visits I, II, III, and IV included collection of diaries (and issuance of the next set of diaries at Treatment Visits I, II and III), and the following efficacy and safety assessments: the site-based Pain Rating Scale, the Neuropathic Pain Scale, the Subject and Clinician Global Impression of Change (Treatment Visit IV only), the SF-36™ Health Status Survey (Acute; Treatment Visit IV only), physical examination (Treatment Visit IV only), vital sign measurements, clinical laboratory tests (Treatment Visits I, III and IV), ECG (Treatment Visit IV only), and ABT-594 plasma assay collection (Treatment Visits I and IV only). A subset of subjects at selected sites underwent additional pharmacokinetic sampling at Treatment Visits I and IV.

On the day after Treatment Visit IV, subjects entered the Post-Treatment Phase. Subjects no longer took study drug or completed pain scales. Subjects could have restarted all discontinued medications under the guidance of their physician. Subjects returned for study procedures at the Follow-Up Visit (7 to 10 days after their final study drug dose). Procedures at the Follow-Up Visit included physical examination, vital sign measurements, recording of any adverse events since Treatment Visit IV, and re-examination of any abnormal ECG or clinical laboratory findings present at the previous evaluation.

For those subjects who participated in clinical studies of ABT-594 and who consented, a blood sample was collected in order to obtain a sample of genetic material (deoxyribonucleic acid [DNA]). The DNA sample may be used at a later date to investigate associations between genetic differences (polymorphisms) and differences in the way subjects respond to treatment, in terms of efficacy or side-effects or both. If a genetic factor in response is identified, it may allow the development of a diagnostic test

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

15

to identify those most likely to benefit before actually taking the drug. The sample may also be used to identify genes involved in painful diabetic polyneuropathy.

Copies of the protocol and amendment, and the CRF are included in Appendices 16.1.1 and 16.1.2, respectively.

9.2 Discussion of Study Design, Including the Choice of Control Groups

The design of this study provided a placebo-control group to assess the analgesic efficacy of ABT-594. Double-blind, parallel-group designs are generally acknowledged as standard for unbiased estimates of treatment group differences. Validated pain scales were employed.

9.3 Selection of Study Population

Approximately 320 subjects were to be randomized and receive study medication in this study. A subject was randomized in this study provided that he/she met all of the inclusion criteria outlined in Section 9.3.1 and did not meet any of the exclusion criteria in Section 9.3.2.

9.3.1 Inclusion Criteria

A subject was to meet all of the following criteria within 22 days before the initial dose of study drug:

1. Prior to any study specific procedure, voluntary written informed consent was obtained from the subject after the purpose and nature of the study were explained.
2. The subject was age 18 or older and in relatively good health with a recent stable medical history.
3. The subject's weight was ≤ 265 pounds.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

16

4. A female subject was to be non-lactating and:

- of non-childbearing potential (either postmenopausal for at least 1 year or surgically sterile, including tubal ligation), or
- of childbearing potential using oral or barrier contraceptive methods for at least 2 months preceding randomization (and continued the contraceptive method through the course of the study).

All female subjects had a negative β subunit human chorionic gonadotropin (β -hCG) at the Baseline Visit. Female subjects of childbearing potential had a negative β -hCG at all Treatment Visits.

5. The subject had a diagnosis of diabetes mellitus (Type I or Type II), a diagnosis of distal symmetric diabetic polyneuropathy, and good control (in the opinion of the investigator) of the subject's serum glucose for at least the last 3 months prior to the Screening Visit.
6. The subject had distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy.
7. The location and quality of the pain under study were consistent with distal symmetric diabetic polyneuropathy in the opinion of the investigator.
8. The subject had distal symmetric diabetic polyneuropathy symptoms (including pain) which were stable for at least the last 3 months prior to the Screening Visit (defined by the opinion of the investigator).
9. The subject had an average of ≥ 4 points on the diary-based Pain Rating Scale (11-Point Likert Scale) during the Baseline Pain Assessment Phase (completed on at least 6 of the 7 days) and ≥ 4 points on the site-based Pain Rating Scale (11-Point Likert Scale) at the Baseline Visit.

9.3.2 Exclusion Criteria

A subject was to be excluded from participation in the study for any of the following reasons:

1. The subject had a positive test result for drugs of abuse or viral hepatitis at the Screening Visit, or had a known history of a positive test result for HIV.
2. The subject had recent (< 5 years) history of drug or alcohol abuse or dependence.
3. The subject had an acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

17

4. The subject had an active malignancy of any type or a history of malignancy (excluding basal cell carcinoma that had been treated or other malignancies that had been surgically removed and had no evidence of recurrence for a minimum of 5 years prior to study start).
5. The subject had taken an investigational drug within 1 month prior to administration of study treatment or was scheduled to receive an investigational drug other than ABT-594 during the course of this study.
6. The subject had a diastolic blood pressure greater than 95 mm Hg and/or a systolic blood pressure greater than 170 mm Hg (sitting) at the Screening Visit.
7. The subject had orthostatic hypotension (defined as a decrease in systolic blood pressure of at least 20 mm Hg or 10 mm Hg in diastolic blood pressure from supine to standing sustained after 1 minute of standing) at the Screening Visit, or a history of syncope or pre-syncope symptoms.
8. The subject had previously participated in a study involving ABT-594, including the present study.
9. The subject had clinically significant abnormalities in clinical chemistry, hematology, or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1.5 times the upper limit of the reference range, a serum creatinine >1.5 mg/dL or a hemoglobin A_{1c} $>11\%$ (subjects may have had elevated serum and urine glucose).
10. The subject had clinically significant electrocardiographic abnormalities.
11. The subject had ongoing treatment with or expected treatment with any medication not allowed as described in Section 9.4.7, including at least 7 days prior to the Baseline Pain Assessment Phase.
12. The subject had a diagnosis of fibromyalgia, arthritis, bursitis, tendinitis, vascular disease or other painful disorders affecting the extremities (other than the neuropathy under study) that the subject could not differentiate from the neuropathy pain.
13. The subject had sympathetically maintained pain (e.g., Reflex Sympathetic Dystrophy, Causalgia), defined by the opinion of the investigator.
14. The subject was unlikely to comply with the study protocol or was unsuitable for any other reason, in the opinion of the investigator.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

18

9.3.3 Removal of Subjects from Therapy or Assessment

A subject could have voluntarily discontinued participation in the study at any time. The investigator may also have decided, for medical reasons or protocol noncompliance, to discontinue prematurely a subject's participation. The investigator was to notify the CRA within 24 hours and document the reason for premature discontinuation on the appropriate CRF.

Subjects whose participation was discontinued prematurely after signing study consent but before study drug administration did not require follow-up observations. Subjects whose participation was discontinued prematurely after study drug administration were to undergo the procedures normally performed at Treatment Visit IV within 7 to 10 days following discontinuation from the study.

If, in the judgment of Abbott Laboratories and possibly in consultation with the investigators, continued exposure to a study drug represented a significant risk to subjects, the study was to be terminated.

9.4 Treatments

9.4.1 Treatments Administered

Subjects were randomly assigned in an equal ratio to 1 of the following 4 treatment groups:

ABT-594 150 µg BID
ABT-594 225 µg BID
ABT-594 300 µg BID
Placebo for ABT-594 BID

ABT-594 and matching placebo were supplied as Light Gray Opaque No. 1 HGCs.

During the Primer Phase, subjects received a fixed dose escalation of study drug. Study drug was initiated at 75 µg BID. The dose was increased every 2 days in 75-µg BID increments until subjects were taking their assigned treatment dose (150 µg, 225 µg, or 300 µg BID). The ABT-594 dose escalation scheme is presented in Table 9.4a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

19

Table 9.4a ABT-594 Dose Escalation

Treatment Group	Suggested Dosing Time	Days 1-7							Day 8
		1	2	3	4	5	6	7	
150 µg	8 AM		75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
ABT-594 BID	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	150 µg	150 µg	150 µg
225 µg	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
ABT-594 BID	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	225 µg
300 µg	8 AM		75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg
ABT-594 BID	8 PM	75 µg	75 µg	75 µg	150 µg	150 µg	225 µg	225 µg	300 µg

During the Primer Phase, subjects randomized to placebo received a fixed dose escalation of placebo BID, in a double-blind fashion.

Subjects started study drug at the PM dose on Day 1 (Section 9.4.5). The number and type of HGCs per dose for the Treatment Phase is presented in Table 9.4b.

Table 9.4b Number and Type of Capsules by Treatment Group

Treatment Group	Number of Capsules Per Dose (Days 8-49)	
	Daily Blister Card (BID doses)	
	75 µg ABT-594 HGC	Placebo ABT-594 HGC
ABT-594 150 µg BID	2	2
ABT-594 225 µg BID	3	1
ABT-594 300 µg BID	4	0
Placebo BID	0	4

9.4.2 Identity of Investigational Product(s)

Information regarding the formulations used in this study is presented in Table 9.4c.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

20

Table 9.4c Identity of Investigational Products

Test Preparation	Drug Product Lot #	Drug Substance Lot #	Source
ABT-594 75 µg HGC Formulation A-2	58-293-AR 61-312-AR	52-015-KD-00	Abbott ^a
Placebo HGC No. 1, Light Gray Opaque (Starch)	55-243-AR-01	not applicable	Abbott ^a

^a PARD Solids Pilot Plant, North Chicago, Illinois.

The ABT-594 75 µg HGC and placebo HGC were identical in appearance.

A listing of subjects receiving test preparations/investigational products from specific batches is presented in Appendix 16.1.6.

9.4.2.1 Packaging and Labeling

Study drug supplies were blinded and packaged in blister cards in accordance with a randomization schedule supplied by Abbott Laboratories (Department of Clinical Statistics). Daily study medication cards were provided to each subject.

Daily study medication cards were labeled with the Module Number (assigned by Abbott, via IVRS), New Product Research Order (NPRO) number, Abbott address, study number, contents, storage conditions and directions for use.

Space was provided on the label of each carton containing the daily study medication cards to record the subject initials and subject randomization number.

9.4.2.2 Storage and Disposition of Supplies

All clinical supplies were stored in a secure location until dispensed to a subject or until returned to Abbott Laboratories. All blinded study drug supplies were stored at controlled room temperature (68-77° F, see USP).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

21

9.4.2.3 Drug Accountability

The investigator or designee verified that study drug supplies were received intact and in the correct amounts. This was documented by signing and dating the Clinical Supplies Invoice or similar document. Study drug was dispensed after randomization and assignment of study medication by IVRS (Section 9.4.3) for each subject who met the enrollment criteria. The investigator or designee recorded the subject number, subject initials, and date the study drug was dispensed to the subject on the Abbott Laboratories Drug Accountability Form. The amount of study drug remaining was recorded at Treatment Visits I, II, III and IV for each subject on the M99-114 Final Drug Supply Reconciliation Summary by Investigator Form. An accurate running inventory of study drug was kept and included the NPRO number, Clinical Supplies Invoice number(s), the number of modules dispensed, and the date study drug was dispensed for each subject. An overall accountability of the study drug was performed and verified by the CRA throughout the study and at the site close-out visit. All supplies (unused and empty blister cards) were inventoried, accounted for, and returned to Abbott Laboratories. A copy of the Return of Investigational Drug Supplies for Disposal Form, in accordance with the instructions of the CRA, was also included in the shipment. The investigator agreed not to supply study medication to any persons not enrolled in the study or not named as a subinvestigator on FDA Form 1572.

9.4.3 Method of Assigning Subjects to Treatment Groups

The randomization schedule was computer-generated before the start of the study by Abbott Laboratories Department of Clinical Statistics. All subjects were centrally randomized by investigative site using an IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site.

Approximately 320 subjects were to be randomized in an equal ratio to receive either ABT-594 150 µg, 225 µg, 300 µg BID or placebo. Subjects were assigned randomization numbers in ascending numerical sequence per investigative site at the Baseline Visit.

The randomization schedule is presented in Appendix 16.1.7.

McCarthy Deposition Exhibit 48

P's Exhibit FZ

Part 2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

22

9.4.4 Selection of Doses in the Study

ABT-594 doses (150 µg, 225 µg, and 300 µg BID) were selected on the basis of Phase I and Phase II studies, and represent doses below the maximally tolerated dose. Phase II data suggested that ABT-594 doses greater than 75 µg BID may be efficacious in the relief of osteoarthritis and distal symmetrical neuropathy pain.

The selection of BID dosing for ABT-594 was based upon Phase I pharmacokinetic results. ABT-594 doses for the Primer Phase (75 µg, 150 µg, and 225 µg BID) were selected based on Phase I safety and pharmacokinetic data.

9.4.5 Selection and Timing of Dose for Each Subject

During the Primer Phase, subjects started study drug at the evening dose on Day 1 within 1 hour following a meal (e.g., 8 PM). Subjects then took BID doses of ABT-594 (75 µg, 150 µg, 225 µg or placebo during the Primer Phase and ABT-594 150 µg, 225 µg, 300 µg or placebo during the Treatment Phase) within 1 hour following a meal (e.g., at 8 AM and 8 PM).

Study drugs were to be taken with at least 1 cup (8 ounces) of water.

9.4.6 Blinding

Both the investigator and the subject remained blinded to the subject's treatment throughout the course of the study. The study blind may have been broken if, in the opinion of the investigator, it was in the subject's best interest to know the study drug assignment. The sponsor was to be notified before breaking the blind, unless identification of the study drug was required for emergency therapeutic measures. Blind breaking information was to be provided using IVRS. Before the study was initiated, the telephone number and call-in directions for the IVRS were provided to each site. The sponsor was to be notified within 48 hours of the blind being broken. The date and reason for blind breakage were to be recorded on the appropriate CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

23

9.4.7 Prior and Concomitant Therapy

At the Screening Visit, a history of medications used over the prior 2 weeks was taken.

Concomitant analgesics (prescription or over-the-counter [OTC], except aspirin and acetaminophen as described below), including (but not limited to) serotonin-specific reuptake inhibitors, mixed serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, antiepileptic medications, sodium channel blockers (e.g., mexilitine), opioids, capsaicin, NSAIDs, COX-2 inhibitors, muscle relaxants, transcutaneous electrical nerve stimulation (TENS) and topical analgesics were not allowed. In addition, St. John's Wort was not allowed.

Aspirin, 325 mg daily maximum, was permitted if taken for primary prevention of thromboembolic events and the dose had been stable for ≥ 1 month prior to the Baseline Visit. Acetaminophen, 3 grams daily maximum, or 6 grams maximum during the Baseline Pain Assessment Phase and per week, for each of the 7 weeks of the Primer and Treatment Phases, was permitted. Subjects were not allowed to take analgesic medication (including acetaminophen) within 24 hours of the Baseline and Treatment Visits I, II, III and IV.

If the administration of any concomitant medication was necessary during the course of this study, the medication name, dosage information, frequency and dates of administration was reported on the CRF. Concomitant analgesic medication use (frequency only) was recorded separately on the Concomitant Analgesic Medication Use CRF at the Baseline Visit and at Treatment Visits I, II, III and IV. The concomitant medication use record included the number of separate occasions each subject had used protocol-allowed (limited amounts) acetaminophen and any other analgesic (taken as a protocol violation) since the subject's previous visit.

9.4.8 Treatment Compliance

In order to document compliance with the treatment regimen, subjects were instructed to return all medication cards and cartons (even if empty) to the study coordinator at Treatment Visits I, II, III and IV. Treatment compliance was documented by the investigator or designee on the M99-114 Final Drug Supply Reconciliation Summary by

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

24

Investigator Form and on the appropriate CRF. Overdose information was collected on the appropriate CRF.

9.5 Efficacy, Pharmacokinetic and Safety Variables

9.5.1 Efficacy, Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Study procedures were performed as summarized in Table 9.5a, Study Procedures Flow Chart.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

25

Table 9.5a Study Procedures Flow Chart

Study Activity	Screening Phase D-22 and D-8	Baseline Pain Assessment Phase D-7 to D-1	Primer Phase D1-D7	Treatment Phase				Post-Treatment Phase D50-D59	
				Treatment Visit					
				D8-D49	D14	D21	D35		D49
Screening Visit	X	D-7 to D-1	Baseline Visit D1	D2-D7					Follow-Up Visit D50 to D59
Uninformed Consent	X		X ^b						X
Medical History	X								X
Physical Exam	X ^c		X ^e						X ^f
Vital Signs	X ^d		X						X ^f
ECG			X						
Clinical Laboratory Tests ^g	X								
Viral Hepatitis Screen	X								
Urine Drug and Alcohol Screen	X								
Pregnancy Test			X				X ^h	X ^h	X ^h
Genetic Polymorphism Sample (If Applicable)			X						
ABT-594 Plasma Assay							X		X
ABT-594 Pharmacokinetic Profile ⁱ							X		X
Diary Initiated	X		X				X	X	
Diary Collected			X				X	X	X
Diary-Based Pain Rating Scale ^j		X		X					
Site-Based Pain Rating Scale			X				X	X	X
Neuropathic Pain Scale			X				X	X	X
Subject/Clinician Global Impression of Change									X
SF-36 [™]			X						X
Randomize Subject									
Dispense Study Drug			X				X ^k	X	
Analgesic Use Monitoring			X				X	X	X
Adverse Event Monitoring			X				X	X	X
Concomitant Medication Monitoring			X				X	X	X
Study Drug Accountability			X				X	X	X
a Or upon premature discontinuation.									
b Interim history.									
c Included height.									
d Included orthostatic measurements at Screening Visit only.									
e Included oral temperature at Baseline Visit only.									
f Performed only if there were clinically significant abnormalities at the previous evaluation.									
g Chemistry, hematology and urinalysis.									
h Required of all females of child-bearing potential.									
i Study drug was to be taken in front of study staff. Blood samples from selected subjects were taken just prior to dosing (0 hour), and at 1.5, 3, 5, and 8 hours after dosing at selected sites only.									
j To be completed at approximately 11 AM each morning during the Baseline Pain Assessment Phase and approximately 3 hours after the morning dose during the Primer and Treatment Phases.									
k Reblinded study medication for days 15-20 after checking drug accountability.									

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ABBT238618

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

26

9.5.1.1 Efficacy Measurements

Prior to any efficacy measurements, a trained site observer instructed the subject on how to perform and record all pain assessments.

The baseline for all efficacy measurements (except for the diary-based Pain Rating Scale) was the last evaluation performed prior to receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study.

Efficacy assessments included the diary- and site-based Pain Rating Scale (11-Point Likert Scale), the Neuropathic Pain Scale, the Subject Global Impression of Change, Clinician Global Impression of Change, and SF-36™ Health Status Survey (Acute).

Efficacy measurements were to be performed 3 to 4 hours post dose, when possible.

Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity daily by completing the Pain Rating Scale in their diaries. These assessments were to be completed daily at approximately the same time each morning (approximately 11 AM) during the Baseline Pain Assessment Phase and daily at the same time each morning (approximately 3 hours after the morning dose of study medication) during the Primer and Treatment phases. Subjects were to record the time they completed the assessments in their diaries.

Subjects also were to assess pain intensity by completing the Pain Rating Scale at the Investigative Site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The time of assessment was recorded on the appropriate CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

27

Neuropathic Pain Scale

The Neuropathic Pain Scale was completed by subjects at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation).

Subject Global Impression of Change

The Subject Global Impression of Change of analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

Clinician Global Impression of Change

The Clinician Global Impression of Change of a subject's analgesic relief due to study drug was performed at Treatment Visit IV (or upon premature discontinuation).

SF-36™ Health Status Survey (Acute)

The SF-36™ Health Status Survey (Acute) was completed by each subject at the Baseline Visit and at Treatment Visit IV (or upon premature discontinuation).

9.5.1.2 Safety Measurements and Procedures

Informed Consent

The investigator or designated representative explained the nature of the study to the subject and answered all questions regarding this study. Prior to any screening procedures being performed on the subject, the informed consent statement was reviewed, signed, and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form was given to the subject and the original was placed in the subject's medical record. An entry was also made in the subject's dated source documents to confirm that informed consent was obtained prior to any study related procedures and that the subject received a signed copy.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

28

Medical History

A complete medical history was obtained from each subject during the Screening Visit. In addition, history of tobacco and alcohol use, and medication (prescription or OTC) use over the 2 weeks prior to screening was recorded. The medical history was updated at the Baseline Visit.

Physical Examination

A physical examination, including weight, was performed at the Screening Visit, Baseline Visit, Treatment Visit IV, and Follow-Up Visit. Height was measured at the Baseline Visit only. The physical examination performed at the Baseline Visit served as the baseline physical examination.

Vital Signs

Blood pressure, pulse rate and respiration rate were measured at the Screening Visit, Baseline Visit, Treatment Visits I, III, and IV, and Follow-Up Visit. Orthostatic blood pressure and pulse rate were measured at the Screening Visit only. Oral temperature was taken at the Baseline Visit only. Vital sign measurements at the Baseline Visit served as the baseline vital sign measurements.

Protocol-specified blood pressure and heart rate measurements (except orthostatic) were obtained after the subject had been sitting for at least 3 minutes. Orthostatic measurements were obtained after 3 minutes in the supine position and then after 1 minute in the standing position. Ideally, the subject's blood pressure was to be measured in the same arm by the same study personnel using the same instrument.

Blood pressure and heart rate measurements were to precede, not follow, scheduled blood draws. Subjects were kept as calm and undisturbed as possible during blood pressure and heart rate measurements.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

29

Electrocardiogram (ECG)

A resting 12-lead ECG was obtained at the Baseline Visit and at Treatment Visit IV. An ECG was performed at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The ECG performed at the Baseline Visit served as the baseline ECG.

A qualified physician interpreted the ECG. One copy of each 12-lead ECG and physician's report was retrieved by the CRA with the CRF.

Clinical Laboratory Testing

Samples were obtained for the clinical laboratory tests presented in Table 9.5b at the Screening Visit, Baseline Visit, and Treatment Visits I, III, and IV. Laboratory tests were obtained at the Follow-Up Visit only if clinically significant abnormalities were present on the previous evaluation. The laboratory test results obtained at the Baseline Visit served as the baseline results (except for hemoglobin A_{1c}, for which the result obtained at the Screening Visit was used as the baseline result). Blood draws were to be performed after pain assessments or vital sign determinations during a visit.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

30

Table 9.5b Clinical Laboratory Tests

Hematology	Blood Chemistry	Urinalysis
Hematocrit	Blood Urea Nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red Blood Cell (RBC) count	Total Bilirubin	pH
White Blood Cell (WBC) count	Aspartate Aminotransferase/ Serum Glutamic-Oxaloacetic Transaminase (AST/SGOT)	Bilirubin
Neutrophils	Alanine Aminotransferase/ Serum Glutamic-Pyruvic Transaminase (ALT/SGPT)	Protein
Monocytes	Lactate Dehydrogenase (LDH)	Blood
Bands	Alkaline Phosphatase	Glucose
Basophils	Sodium	Microscopic evaluation
Eosinophils	Potassium	
Lymphocytes	Chloride	
Hemoglobin A _{1c} (Screening Visit and Treatment Visit IV only)	Calcium	
Mean Corpuscular Hemoglobin (MCH)	Inorganic Phosphorus	
Mean Corpuscular Hemoglobin Concentration (MCHC)	Uric Acid	
Mean Corpuscular Volume (MCV)	Bicarbonate	
Platelet count (estimate was not acceptable)	Cholesterol	
Prothrombin Time (PT)	Total Protein	
Partial Thromboplastin Time (PTT)	Glucose	
	Triglycerides	
	Albumin	

A central laboratory was utilized to process and provide results for the clinical laboratory tests.

The investigator reviewed all laboratory test results and assessed the clinical significance for each abnormal result. All laboratory test results that were considered clinically significant by the investigator were followed to satisfactory resolution. A copy of each laboratory report was included with the CRF.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

31

Viral Hepatitis Screen

At the Screening Visit, subjects underwent serological evaluation for viral hepatitis (hepatitis A virus IgM antibody, hepatitis B virus surface antigen, and hepatitis C virus antibody). The hepatitis test panel was performed by the central laboratory.

Urine Drug Screen and Alcohol Screen

Urine specimens, collected at the Screening Visit, were tested for drugs of abuse and alcohol by the central laboratory.

Pregnancy Test

A urine pregnancy test was performed by designated study personnel at the Baseline Visit for all female subjects and at Treatment Visits I, II, III, and IV for female subjects of childbearing potential. A lactating or pregnant female was not eligible for participation in this study.

Adverse Events

An adverse event is defined as any unexpected event(s) such as a disease, syndrome, sign, symptom, and/or laboratory finding associated temporally with the use of drug in humans, whether or not thought to be drug-related and whether observed by the investigator or reported by the subject. Subjects were instructed to contact the investigator if an adverse event occurred so that appropriate action could be taken.

All adverse events, whether in response to a query, observed by site personnel, or spontaneously reported by the subject were reported on the appropriate CRF. All adverse events and post-treatment laboratory abnormalities considered clinically significant by the investigator were followed to a satisfactory resolution.

The investigator assessed and recorded any adverse event in detail on the adverse event CRF including the date of onset, description, final diagnosis (if known), severity,

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

32

time course, duration and outcome, relationship of the adverse event to study drug, an alternate etiology for the event, and action taken. For adverse events to be considered as sporadic, the events must have been of a similar nature and severity.

The investigator used the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on rechallenge and another etiology is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator opinion of possibly related, probably not related, or not related to study drug was given, an alternate etiology was provided for the adverse event.

Adverse events (including those that met regulatory criteria for a serious adverse event) were monitored continuously from the time of study drug administration to the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

33

Follow-Up Visit. In addition, adverse events spontaneously reported to the investigator after completion of the Treatment Phase (or after premature discontinuation) were collected up to 30 days after drug discontinuation and reported to Abbott Laboratories. Subjects were instructed to report to the investigator any other adverse events that occurred after the Follow-Up Visit.

Serious adverse events, as well as adverse events that the investigator considered to be related to study design and/or procedures, that occurred after signing the informed consent and prior to the first dose of study drug were also collected.

Any abnormal laboratory value or change in vital signs was not documented as an adverse event unless it was a reason for premature discontinuation from the study, required treatment, or met regulatory criteria for a serious adverse event.

Ongoing medical conditions were considered adverse events if there was an increase in severity or frequency of occurrence. Since measurements of pain intensity were efficacy measurements in this study, an increase in severity or frequency of occurrence of the pain under study was not considered an adverse event for the purposes of this study.

Serious Adverse Events

If an adverse event met any of the following criteria, whether related to study drug or not, the investigator and other professional personnel in attendance was to be notified as soon as possible for the appropriate action. The investigators were to notify Abbott Laboratories by telephone within 24 hours of being made aware of any serious adverse event. In addition, a written confirmation of the occurrence, including any supplementary data, was to be sent within 3 days of the telephone report.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

34

Death of Subject:	An event which results in the death of a subject.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in fatality if immediate medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an admission to the emergency room or outpatient facility.
Prolongation of Hospitalization:	An event which occurs while the study subject is hospitalized and that prolongs the subject's hospital stay.
Persistent or Significant Disability/Incapacity:	An event which results in a condition that interferes with the activities of daily living of a study subject (e.g., permanent loss of vision).
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that, based on medical judgement, may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in the "serious" definition (e.g., allergic bronchospasm requiring intensive treatment in the home or emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

In addition, miscarriage/spontaneous and elective abortions were to be reported to Abbott Laboratories as serious adverse events.

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ABBT238627

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

35

9.5.2 Appropriateness of Measurements

All efficacy measurements in this study were validated and considered standard for this population. All clinical and laboratory procedures in this study were standard and generally accepted.

9.5.3 Efficacy Variables

9.5.3.1 Primary Variable

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug. The baseline pain score for the diary data was defined as the average of the last 7 pain scores prior to receiving the first dose of blinded study drug on Day 1 of the study.

9.5.3.2 Secondary Variables

Change from baseline to final and each scheduled evaluation was calculated for each of the following secondary efficacy variables:

- Diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each evaluation only
- Site-based Pain Rating Scale (11-Point Likert Scale)
- Neuropathic Pain Scale
- Subject Global Impression of Change
- Clinician Global Impression of Change
- SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health]⁷ physical component summary (PCS), and mental component summary (MCS).⁸

The pain evaluations recorded at the Baseline Visit were used as the baseline score for pain evaluations assessed at the investigative site.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

36

9.5.4 Drug Concentration Measurements

Blood samples for ABT-594 plasma assay were to be collected from all subjects at Treatment Visits I and IV. One blood sample (approximately 7 mL) was to be collected into a sodium heparin evacuated collection tube at each visit. Blood draws were to be performed after any pain assessments or vital sign determinations during a visit. For subjects who prematurely discontinued, a blood sample was to be taken for ABT-594 assay at the premature discontinuation visit, and the exact time at which the prior dose was taken was to be recorded.

For those subjects participating in the additional pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), blood samples were collected at Treatment Visits I and IV.

After establishing the time of the Treatment Visit, the subject was instructed to take the preceding day's study drug as close as possible to 8 PM. At the office visit, the study medication was taken in the presence of the office staff in order to allow proper and accurate recording of blood collection times relative to dosing. The time of the visit accommodated a target time for the morning dose of 12 hours after the preceding evening's dose. Blood samples were collected as follows: just prior to dosing (0 hour) and at 1.5, 3, 5, and 8 hours after the morning dosing. Subjects received their 8 PM dose as scheduled. Subjects were confined at the site until the 8-hour blood sample was collected.

All blood samples were immediately stored at 4°C or below. The samples were to be separated by centrifugation within 1 hour after collection. The supernatant was to be transferred by polypropylene pipettes into plastic vials clearly marked as "Assay Plasma" and labeled with the study drug number, protocol number, subject number, initials, and date and time of sample collection. This information was also recorded on the appropriate CRF. All labeled plastic vials were placed in a rack to prevent breakage. Plasma samples for determination of ABT-594 were frozen at -5°C or colder within 1 hour from

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

37

centrifugation. All specimens were kept frozen at -5°C or colder until packed in solid carbon dioxide (dry ice) for shipment to Abbott Laboratories.

The time and date of each subject's morning dose on the days of plasma assay blood draws, the time and date of the meal eaten prior to the morning dose, and the time and date of the evening dose on the day prior to the plasma assay blood draws were recorded on the CRF.

Details of the ABT-594 assay methodology will be presented in the Clinical Pharmacokinetic Report.

9.5.5 Pharmacokinetic Variables

For the subset of subjects who underwent additional pharmacokinetic sampling at Treatment Visits I and IV, values of AUC, C_{max} , and C_{trough} were to be calculated using noncompartmental methods.

9.5.6 Blood Samples for Genetic Polymorphism Analysis

Two 10 mL whole blood samples were collected in purple top (EDTA) tubes at the Baseline Visit and shipped immediately at ambient or refrigerated temperature to Covance Central Laboratory Services.

If clear differences in response are noted during the clinical development of ABT-594 and believed to be genetically related, these samples may be analyzed as part of a multicenter, multistudy project to identify genetic factors involved in the response to ABT-594 or drugs of this class. The specific response may be related to efficacy or safety, or both. The results of this potential analysis are not reported with this study summary. The samples may also be used for development of a diagnostic test for drug response.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

38

9.6 Data Quality Assurance

Prior to the initiation of this protocol, an investigator's meeting was held with Abbott personnel, the investigators and their study coordinators, the CRO's project manager and CRAs. This meeting entailed a detailed discussion of the protocol, CRF completion, and specimen collection methods. In addition to the investigator's meeting, the study personnel at each site were trained on the study procedures by a CRA at a study initiation visit and given a CRF completion workbook for reference. The CRAs monitored each site approximately every 4 weeks. At each visit, 100% source-document review was made against the entries on the CRFs and a quality-assurance check was performed to ensure that the investigator was complying with the protocol and regulations. The investigator agreed to provide Abbott Laboratories (or designee) access to all source documents in order to verify CRF entries. In addition, after CRFs were retrieved by the CRA, a review of the data was conducted by a physician and a clinical review team at Abbott Laboratories.

The SF-36™ Health Status Survey (Acute) was recorded directly on the CRF and was considered source data.

All CRFs were to be legible and completed in black ball point ink. All corrections were initialed and dated by the investigator or designated assistant. The investigator reviewed the CRFs for completeness and accuracy and signed and dated the set of CRFs where indicated.

Each CRF was printed on 3-part no carbon required (NCR) paper. The forms consisted of a white, yellow and pink copy. The white and yellow copies of the completed, verified CRF were collected by the CRA and the pink copy was retained at the investigative site.

Data captured on the CRF were entered into the database by a double-key entry procedure at Abbott Laboratories. Discrepancies against the hard-copy CRF were reviewed and corrected on-line. After completion of the entry process, computer logic checks were run to check for such items as inconsistent study dates and outlying laboratory values, and any

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

39

necessary corrections were made to the database and documented via addenda or audit trail.

The laboratory results were electronically transferred from the central laboratory to the study database. A final review of all laboratory results was conducted by a physician and clinical review team at Abbott Laboratories.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

All statistical tests were 2-tailed and considered statistically significant if the P-value (Type 1 error rate) was less than or equal to 0.05 (when rounded to 3 decimal places).

For all efficacy and safety endpoints, comparisons of primary interest were between each ABT-594 treatment group and the placebo group, along with an assessment of ABT-594 linear dose response. Appropriate secondary comparisons were to be made as considered necessary. No statistical adjustments were made for multiple comparisons.

The baseline for all variables (except for the diary-based Pain Rating Scale) was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline measurement for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to the subject receiving the first dose of blinded study drug on Day 1.

9.7.1.1 Data Sets Analyzed

Efficacy analyses were to be performed for 2 sets of data: intent-to-treat (ITT) subjects and evaluable subjects. Subjects who received at least 1 dose of study drug with at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale) were included in the ITT analyses. The evaluable dataset included subjects who received at least 7 days of

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

40

study drug with at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. Safety analyses were performed with all randomized subjects who received at least 1 dose of study drug.

9.7.1.2 Demographic and Other Baseline Characteristics

Baseline comparability among treatment groups for the reasons for premature discontinuation, demographic and baseline pain assessment measurements was assessed. The analyses were performed using 1 or more of the following methods: a 1-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables, the Cochran-Mantel-Haenszel (CMH) test for equal row means for ordered categorical variables, and the Fisher's exact test (or its generalization to $r \times c$ tables) for qualitative variables.

9.7.1.3 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to the subject receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the average of the last 7 pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

Primary Efficacy Analysis

The primary efficacy measurement was the change from baseline of the average diary-based Pain Rating Scale (11-Point Likert Scale) score from each subject's diary to the corresponding average of the last 7 days on study drug.

Treatment groups differences for the primary efficacy variable were evaluated using a 2-way ANOVA with factors for treatment group, study center, and the treatment group by study center interaction. If the interaction term was not statistically

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

41

significant at the 0.10 level, the primary efficacy analysis for the treatment group differences was to be the 2-way ANOVA with factors for treatment group and study center, but without the interaction term. If some study centers had fewer than 1 subject per treatment group in the ITT dataset, data from such centers were to be combined for analysis.

Secondary Efficacy Analysis

Treatment group differences in the mean change from baseline to the final evaluation for the Neuropathic Pain Scale, SF-36™ Health Status Survey (Acute), including 8 sub-domains and PCS and MCS, and the site-based Pain Rating Scale (11-Point Likert Scale) score were assessed using a 2-way ANOVA as described in the above Primary Efficacy Analysis subsection. The actual scores of each of the Subject and Clinician Global Impression of Change were analyzed using the CMH test for equal row means with study centers as strata. SF-36™ PCS and MCS could have also been analyzed using appropriate regression analysis (with possible factors for demographic variables, treatment and time).

Additionally, treatment group differences in the change from baseline to each scheduled evaluation were assessed, as described for the change from baseline to the final evaluation for the Neuropathic Pain Scale and the site-based Pain Rating Scale (11-Point Likert Scale). For the diary-based Pain Rating Scale (11-Point Likert Scale), change from baseline to each scheduled evaluation was analyzed using the last 7 days prior to each scheduled visit. Subject and Clinician Global Impression of Change was evaluated using CMH methodology on actual scores.

If indicated, exploratory analyses were to be performed on change from baseline pain scores, such as analysis of covariance (ANCOVA), with baseline pain scores as the covariate.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

42

Dose response for ABT-594 was explored using both a parametric regression model and nonparametric tests, with and without placebo included. If the effect of investigator sites was not significant, then the nonparametric Jonckheere-Terpstra test was to be used instead of Page's test to assess dose response of ABT-594.

Other analyses were to be performed as appropriate.

Missing Data

Two sets of analyses, corresponding to the handling of missing observations, were performed on the efficacy variables. The "last observation carried forward" (LOCF) analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had data for each specified evaluation. This technique reduces the bias caused by subjects who prematurely discontinue for lack of efficacy. The "observed cases" (OC) analysis did not estimate the missing evaluation, and a subject who did not have pain evaluation on a scheduled visit was excluded from the OC analysis for that visit.

In the event of data missing from the individual items in the Neuropathic Pain Scale and SF-36™ Health Status Survey (Acute), the estimated score of the missing item was calculated, when less than ½ (within the scale of interest) of items are non-missing, as follows:

1. Calculate the ratio of the total score of the scale (the non-missing items) divided by the maximum possible total score for the non-missing items,
2. Multiply the maximum possible scores for the missing item by the ratio obtained in Step 1 above.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

43

9.7.1.4 Pharmacokinetic Analyses

The maximum observed plasma concentration (C_{\max}), the time to C_{\max} (T_{\max}), and the trough plasma concentration (C_{trough}) were to be obtained directly from the plasma concentration-time data. The area under the plasma concentration-time curve during a dosing interval (AUC) were to be obtained by the trapezoidal rule, using the Hour 0 concentration value for the Hour 12 value, or by some other appropriate methodology.

To assess dose proportionality and time invariance, T_{\max} , dose-normalized C_{trough} and log-transformed dose-normalized AUC and C_{\max} from the subset of subjects participating in the additional pharmacokinetic sampling were to be subjected to a mixed effects model analysis. The model was to include dose, visit (Treatment Visit I and Treatment Visit IV), and dose by visit interaction as fixed effects. Age, body weight, nicotine-use status, and other variables that may have accounted for variability in pharmacokinetics were to be included as covariates. The study center factor was to be included in the initial model, including a center main effect and, interaction of center with other factors. The center factor, or at least the interaction terms involving center, were to be dropped from the model if they explained little of the variability in the data. If the number of subjects who had only Treatment Visit I data and not Treatment Visit IV data exceeded 20% of the subjects with additional pharmacokinetic sampling, then the analyses were also to be performed for each visit separately. The hypothesis of invariance with dose was to be tested by comparing the 300 μg BID dose versus the 150 μg BID dose. If the hypothesis of dose proportionality was rejected in a comparison, then the 225 μg BID dose was to be compared to each of the 150 and 300 μg BID doses. If the visit by dose interaction was statistically significant, then a comparison was to be made for each visit.

An exploratory analysis was also to be performed on the data set obtained from all subjects (including those who did not participate in the additional pharmacokinetic sampling). This analysis was to take into account the appropriate time of sampling

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

44

relative to dosing. The questions of dose proportionality and change from Treatment Visit I to Treatment Visit IV were to be considered in this analysis.

If there was some evidence from the data of this study that ABT-594 was efficacious, then the relationship between ABT-594 plasma concentration and the primary efficacy variable was to be explored, using data from ABT-594 and placebo treatment groups or from ABT-594 treatment groups alone. One exploration was to utilize the data of all subjects. An analysis using only the data of subjects undergoing additional pharmacokinetic sampling was also to be performed. The model was to include effects for efficacy variable baseline value and for visit. The center factor was to be incorporated appropriately. The dependency of the measurements from the same subject was to be accounted for. Other analyses were to be performed as necessary.

9.7.1.5 Safety Analyses

All subjects who received at least 1 dose of study drug were evaluated for safety.

Adverse events were coded using the COSTART V9 dictionary. Treatment-emergent adverse events (i.e., those which began or worsened in severity after randomized study drug was taken) were tabulated by body system and COSTART term for each treatment group. Treatment group differences were evaluated using Fisher's exact test for the proportion of subjects reporting a particular adverse event. A summary of the severity, relationship to study drug, incidence and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group. Analyses by subgroup were performed as appropriate.

Laboratory data were analyzed using a 1-way ANOVA with treatment as the main effect. The primary analyses were the change from baseline to the minimum, maximum, and final values during the study for each laboratory variable.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

45

Additionally, the number and percentage of subjects with shifts from baseline to the final values using criteria for limits for statistical analysis and normal ranges to define categories (low, normal, high and missing) was summarized.

Laboratory data values were categorized as low, normal, or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values were flagged in the data listings. In addition, laboratory results which satisfied the criteria for limits for statistical analysis were identified.

Mean changes from baseline to the minimum, maximum and final values for vital signs and ECG were analyzed in a similar manner as described for laboratory data above. Vital sign and ECG results which satisfied the criteria for below and above limits were identified.

Concurrent medication use was summarized by treatment group.

Additional safety analyses were to be performed as indicated.

9.7.2 Determination of Sample Size

The study was designed to enroll approximately 320 subjects (approximately 80 subjects in each treatment group). This sample size should have allowed for the detection of a 0.46 effect size in the average diary-based Pain Rating Scale score for change from baseline to the final evaluation between any ABT-594 treatment group and placebo at 0.05 (two-tailed Type I error) level with at least 80% power. This calculation was based on results obtained from Study M98-8336 of ABT-594 and published data using Gabapentin for subjects with painful diabetic polyneuropathy¹⁰ and assuming a 39% and 25% improvement from baseline for ABT-594 and placebo, respectively.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

46

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Protocol Changes

Significant changes in the developmental strategy of ABT-594 resulted in the study being prematurely discontinued by the sponsor. Therefore, although the protocol specified that approximately 320 subjects (80 per treatment group) were to be enrolled, enrollment was stopped at 266 subjects.

The final clinical protocol incorporated Amendment Number 1. All subjects were enrolled under the final protocol (Table 14.1__2). Full details of the clinical protocol and its amendment are presented in Appendix 16.1.1. Important changes included in the amendment are summarized below:

Amendment 1 (29 February 2000)

- Modified the inclusion criteria such that subjects were required to have good control (in the opinion of the investigator) of their serum glucose for at least the last 3 months prior to the Screening Visit.
- Added that subjects with a hemoglobin A_{1c} >11% were to be excluded.
- Added hemoglobin A_{1c} at the Screening Visit and Treatment Visit IV and deleted the hemoglobin A_{1c} at the Baseline Visit.
- Added mixed serotonin and norepinephrine reuptake inhibitors and St. John's Wort to the list of excluded medications.
- Added that the Screening hemoglobin A_{1c} result served as the baseline result.

9.8.2 Statistical Changes

Although not specified in the protocol, efficacy analyses were also performed on a dataset that included subjects who did not prematurely discontinue from the study (study completers).

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

47

The change from baseline of the average diary-based Pain Rating score from each subject's diary to the corresponding average of each of the consecutive 7-day intervals after the first dose of study drug was summarized using both LOCF and OC techniques.

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to final, was analyzed for the following variables: diary- and site-based average Pain Rating Scale scores and Neuropathic Pain Scale Total Scores. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

10.0 Study Subjects

10.1 Disposition of Subjects

The location of premature discontinuation data is presented below.

Assessment	Statistical Analyses Table	Individual Subject Listing Appendix
Number and Percentage of Subjects Prematurely Discontinued	14.1__3.1	16.2__1.1
Listing of Subject Numbers by Reason for Premature Discontinuation	14.1__3.2	16.2__1.1
Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued	14.1__3.3	16.2__1.1 16.2__7.1.1
Number of Subjects Who Prematurely Discontinued by Days of Exposure to Study Drug	14.1__3.4	16.2__1.1 16.2__5.1.1 16.2__5.1.2
Number and Percentage of Subjects that Prematurely Discontinued for Each Investigator	14.1__3.5	16.2__1.1
Previous and Concurrent Medications (Subjects Who Prematurely Discontinued)	none	16.2__1.1 16.2__1.2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

48

Two hundred sixty-six (266) subjects were enrolled by 29 investigators. Of the 266 subjects, 65 were randomized to receive placebo, 65 were randomized to receive ABT-594 150 µg BID, 69 were randomized to receive ABT-594 225 µg BID, and 67 were randomized to receive ABT-594 300 µg BID. All 266 subjects who received study drug are included in the analyses of all treated subjects. Additionally, 3 subjects were randomized although they failed to meet admission criteria. These subjects did not receive study drug and are not included in the database.

The proportion of subjects prematurely discontinuing from the study was statistically significantly different among the treatment groups, with 14 (22%) subjects in the placebo treatment group, 25 (38%) subjects in the ABT-594 150 µg BID treatment group, 39 (57%) subjects in the ABT-594 225 µg BID treatment group, and 50 (75%) subjects in the ABT-594 300 µg BID treatment group. A statistically significant difference was also observed among the treatment groups for the proportion of subjects prematurely discontinuing from the study due to 1 or more adverse event, which was the most frequently reported reason for premature discontinuation (9% placebo, 28% ABT-594 150 µg BID, 46% ABT-594 225 µg BID, and 66% ABT-594 300 µg BID). Subject disposition is presented in Table 10.1a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

49

Table 10.1a Disposition of Subjects

	Treatment Group n (%)			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
All Treated Subjects	65	65	69	67
Completed Study	51 (78%)	40 (62%)	30 (43%)	17 (25%)
Prematurely Discontinued ^a	14 (22%)	25 (38%)	39 (57%)	50 (75%)
Adverse Event	6 (9%)	18 (28%)	32 (46%)	44 (66%)
Lack of Efficacy	6 (9%)	6 (9%)	2 (3%)	5 (7%)
Withdrew Consent	2 (3%)	3 (5%)	6 (9%)	5 (7%)
Subject Noncompliant	1 (2%)	3 (5%)	4 (6%)	2 (3%)
Lost to Follow-up	0	0	1 (1%)	2 (3%)
Other ^b	1 (2%)	1 (2%)	3 (4%)	2 (3%)

^a Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

^b Description of reason designated as "other": subject stopped taking study drug (2 subjects), initiation of exclusionary medication, medical records noting subject is an alcoholic, refusal to return for follow-up, out of town for 6 weeks, and randomization error (1 subject each).

Cross Reference: Tables 14.1__3.1 and 14.1__3.3 and Appendix 16.2__1.1

A graphic disposition of all subjects is presented in Figure 10.1a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

50

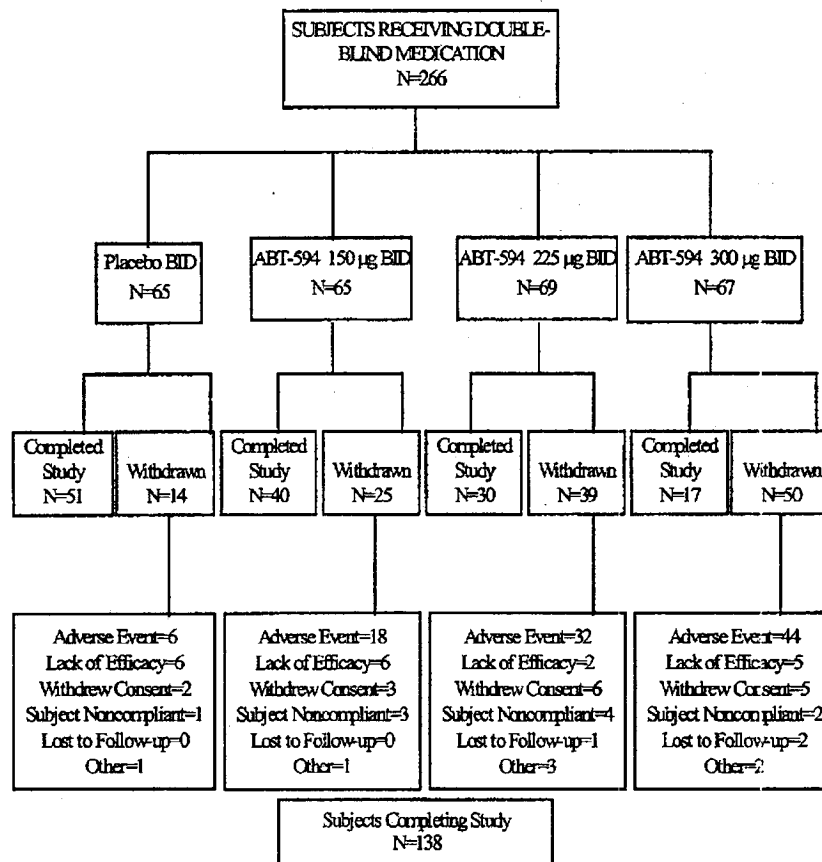


Figure 10.1a Disposition of Subjects

Note: Subjects may have reported more than 1 reason for premature discontinuation, but were counted only once in the total.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

51

10.2 Protocol Deviations

The location of protocol deviation data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Admission Criteria	none	16.2_2.1
Blind Broken	none	16.2_1.3
Urine Drug Screen	none	16.2_2.2
Hepatitis Screen	none	16.2_2.3
Pregnancy Test Results	none	16.2_2.4
Other Medications and Supplements	none	16.2_7.3

In reviewing the data for all subjects, deviations from the protocol were identified. Clinically significant inclusion/exclusion criteria deviations included the following: failure to perform a pregnancy test at the Baseline Visit (19 subjects), current or expected use of an exclusionary medication (10 subjects), failure to have an average of ≥ 4 points on the diary-based Pain Rating Scale during the Baseline Pain Assessment Phase and ≥ 4 points on the site-based Pain Rating Scale at the Baseline Visit (6 subjects), acute or chronic renal or hepatic disorder, psychiatric disease or disorder or any uncontrolled medical illness (2 subjects), and failure to have distally and symmetrically decreased or lost vibratory, pin and/or light touch sensation on neurological exam and either decreased (or absent) deep tendon reflexes or documented abnormal nerve conduction study consistent with a distal symmetrical neuropathy (2 subjects). These and other minor deviations were not considered important enough to affect the outcome of the study.

One hundred twenty (15 placebo, 30 ABT-594 150 μg , 34 ABT-594 225 μg , and 41 ABT-594 300 μg BID) of the 266 subjects (45%) did not have at least 1 blood sample collected for pharmacokinetic analysis. The remaining 146 subjects (55%) had at least 1 blood sample collected. At the time of this report, the pharmacokinetic analyses were incomplete. Results from the pharmacokinetic analyses will be presented in a separate report.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

52

Study drug dosing errors were noted for 3 subjects. At the Baseline Visit, Primer Phase modules 17011 and 17001 were incorrectly dispensed to Subjects 4136 (placebo) and 4134 (ABT-594 150 µg BID), respectively. These subjects took incorrect study drug on Study Days 1 through 7. The subjects were also dispensed Treatment Phase modules at the same visit and these modules were dispensed correctly. Therefore, subjects 4136 and 4134 were each taking their correct randomized dose beginning on Study Day 8. One subject (4099) randomized to ABT-594 225 µg BID actually received ABT-594 300 µg BID (module 30157) on Study Days 21 through 37 (Appendix 16.2__5.1.1). In all efficacy and safety analyses, data for Subject 4099 were included in the ABT-594 225 µg BID treatment group.

11.0 Efficacy and Pharmacokinetic Evaluation

11.1 Data Sets Analyzed

The 266 randomized subjects who received at least 1 dose of study drug comprise the “all treated subjects” dataset and are included in the safety analyses. The primary efficacy dataset was the ITT dataset, which included all randomized subjects who took at least 1 dose of study drug and had at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). Of the 266 all treated subjects, 251 were included in the ITT dataset (Tables 14.2__1.1 and 14.2__1.2).

In addition, efficacy analyses based on “evaluable” and “completers” data were performed. The 217 subjects who received at least 7 days of study drug and who had at least 1 pre-dose pain assessment and at least 1 post-Day 7 pain assessment for the diary-based Pain Rating Scale comprised the “evaluable” efficacy dataset (Tables 14.2__8.1 and 14.2__8.2). The 138 subjects who did not prematurely discontinue from the study for any reason were included in the completers data set. Efficacy ITT, evaluable, and completer exclusions are identified in the data listings.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

53

The treatment groups were similar with respect to the number and percentage of subjects contributed by each investigator in the ITT and evaluable datasets (Table 14.1__1.2).

A summary of subject accountability is presented in Table 11.1a.

Table 11.1a Disposition of Subjects by Dataset

	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Number of Subjects Planned	80	80	80	80
Number of Subjects Randomized	65	65	69	67
Subjects Included in the All Treated Subjects Dataset	65	65	69	67
Subjects Included in the Intent-to-Treat Dataset	62	61	66	62
Subjects Included in the Efficacy Evaluable Dataset	61	53	54	49
Subjects Included in the Completers Dataset	51	40	30	17

Cross Reference: Table 14.1__1.2 and Appendices 16.2__3.1, 16.2__3.2, and 16.2__3.3

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

54

11.2 Demographic and Other Baseline Characteristics

All demographic and other baseline characteristic results are for all treated subjects, unless otherwise specified. The location of demographic and other baseline characteristic data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Demographics	14.1__4.1	16.2__4.1
Medical History	14.1__5.1 14.1__5.2	16.2__4.2
Nicotine Consumption	14.1__4.1	16.2__4.3
Baseline Pain Assessments	14.1__6	16.2__6.2.1 16.2__6.2.2 16.2__6.3.1 16.2__6.3.2 16.2__6.4.1 16.2__6.4.2 16.2__6.4.3

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

55

11.2.1 Demographics

No statistically significant differences were observed among treatment groups for sex, race, age, height, or weight. The average age was 61.9 years (range = 20 - 86 years). Eighty-nine percent of the subjects were white. Subject demographic characteristics are presented in Table 11.2a.

Table 11.2a Demographic Characteristics (All Treated Subjects)

Demographic Characteristic	Treatment Group n (%)				p-value ^a
	Placebo (N=65)	ABT-594			
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)	
Sex					0.870
Female	27 (42%)	31 (48%)	33 (48%)	30 (45%)	
Male	38 (58%)	34 (52%)	36 (52%)	37 (55%)	
Race^b					0.751
White	57 (88%)	58 (89%)	64 (93%)	59 (88%)	
Black	7 (11%)	6 (9%)	3 (4%)	8 (12%)	
Asian	0	1 (2%)	1 (1%)	0	
Native	0	0	1 (1%)	0	
American	1 (2%)	0	0	0	
Other					
Age (years)					0.110
Mean (SD)	60.2 (11.43)	60.8 (10.78)	61.8 (11.80)	64.7 (11.10)	
Min-Max	20 - 80	36 - 85	24 - 84	31 - 86	
Height (inches)^c	(N=65)	(N=65)	(N=69)	(N=66)	0.300
Mean (SD)	68.4 (4.47)	67.5 (3.93)	67.1 (4.27)	67.3 (3.73)	
Min-Max	60 - 77	59 - 75	59 - 79	60 - 75	
Weight (pounds)^c					0.758
Mean (SD)	205.3 (36.44)	200.0 (40.03)	199.2 (34.57)	203.1 (34.94)	
Min-Max	127.9 - 275.0	113.0 - 276.0	112.0 - 258.0	134.5 - 277.8	

^a p-values are from extension of Fisher's exact test comparing treatment groups (sex, race), or a 1-way ANOVA model comparing treatment groups (age, height, and weight).

^b Non-white races were combined for calculation of p-value. American Indian/Alaska Native was represented as Native American.

^c At baseline.

Cross Reference: Table 14.1 __ 4.1 and Appendix 16.2 __ 4.1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

56

11.2.2 Other Baseline Characteristics

There were no statistically significant differences among treatment groups in the ITT analysis with respect to all pain assessment variables (including diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score) and other baseline characteristics including nicotine use. The baseline characteristics for the ITT dataset are presented in Table 11.2b.

Pain assessment scales are presented in Appendix 16.1.13.

Table 11.2b Other Baseline Characteristics (Intent-to-Treat Dataset)

Baseline Characteristic	Treatment Group				p-value ^a
	Placebo	ABT-594			
		150 µg BID	225 µg BID	300 µg BID	
Diary-Based Pain Scale ^b	(N=62)	(N=64)	(N=67)	(N=66)	0.847
Baseline Mean (SD)	6.5 (1.43)	6.6 (1.69)	6.7 (1.51)	6.7 (1.74)	
Site-Based Pain Scale ^b	(N=64)	(N=64)	(N=69)	(N=66)	0.608
Baseline Mean (SD)	6.5 (1.67)	6.7 (1.98)	6.7 (1.57)	6.9 (1.91)	
Neuropathic Pain Scale Total Score ^c	(N=64)	(N=65)	(N=69)	(N=64)	0.910
Baseline Mean (SD)	56.5 (17.47)	55.1 (17.47)	56.3 (15.18)	57.3 (19.81)	
Nicotine Used	(N=65)	(N=65)	(N=69)	(N=67)	0.098
Former User	29 (45%)	24 (37%)	18 (26%)	25 (37%)	
Non-User	32 (49%)	31 (48%)	40 (58%)	38 (57%)	
Current User	4 (6%)	10 (15%)	11 (16%)	4 (6%)	

a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).

b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.

d Former users and non-users were combined for calculation of p-value.

^a p-values are from extension of Fisher's exact test comparing treatment groups (nicotine use) or 1-way ANOVA model comparing treatment groups (pain scores).

^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

^c Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = most.

^d Former users and non-users were combined for calculation of p-value.

Cross Reference: Tables 14.1_4.1, 14.1_6 and Appendices 16.2_4.3, 16.2_6.2.1, 16.2_6.2.2, 16.2_6.3.1, 16.2_6.4.1, 16.2_6.4.2, and 16.2_6.4.3

A medical history was obtained for each subject who entered the study. Among currently symptomatic subjects, sporadic statistically significant differences were observed between each of the ABT-594 150 µg BID and 300 µg BID treatment groups and the placebo

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

57

treatment group for the proportions of subjects who had a specific condition/diagnosis (Table 14.1__5.1). Among currently asymptomatic subjects, no apparent differences were observed between treatment groups for the proportion of subjects with a specific condition/diagnosis (Table 14.1__5.2).

11.2.3 Concurrent Medication Use

The proportion of subjects using a concomitant medication during the study was similar among treatment groups. The number and proportion of subjects who took concomitant medications during the study and listing of subject numbers by therapeutic classifications are presented in Tables 14.1__7.1 and 14.1__7.2, respectively. Individual subject data listings for subjects who took previous and concomitant medications are presented in Appendix 16.2__7.3.

During the Baseline Pain Assessment Phase, no statistically significant difference was observed among treatment groups for the proportion of subjects who used protocol-allowed concomitant analgesic medication (Table 14.2__7.1).

11.3 Measurements of Treatment Compliance

The location of compliance and drug concentration data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Study Drug Administration	14.1__8	16.2__5.1.1 16.2__5.1.2
Plasma Assay	none	16.2__5.3.1 16.2__5.3.2

11.4 Efficacy Evaluations and Tabulations of Individual Subject Data

Each efficacy analysis compared the placebo treatment group versus each of the other ABT-594 treatment groups. Efficacy scale ranges are presented in Appendix 16.1.13.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

58

11.4.1 Efficacy Analyses

The location of efficacy data is presented below.

Assessment	Statistical Analyses Tables ^a	Individual Subject Listing Appendix
Diary-Based Pain Rating Scale	14.2_2.1.1.1	16.2_6.2.1
	14.2_2.1.1.2	
	14.2_2.1.2	
	14.2_2.1.3	
	14.2_2.1.4	
	14.2_2.2	
	14.2_2.3	
	14.2_2.4.1.1	
	14.2_2.4.1.2	
	14.2_2.4.2	
	14.2_2.4.3	
	14.2_2.4.4	
Site-Based Pain Rating Scale	14.2_3.1.1	16.2_6.2.2
	14.2_3.1.2	
	14.2_3.1.3	
	14.2_3.2	
	14.2_3.3	
	14.2_3.4	
Neuropathic Pain Scale	14.2_4.1.1	16.2_6.3.1
	14.2_4.1.2	16.2_6.3.2
	14.2_4.1.3	
	14.2_4.1.4	
	14.2_4.2	
	14.2_4.3	
	14.2_4.4	
Global Impression of Change	14.2_5.1	16.2_6.5
	14.2_5.2	
	14.2_5.3	
	14.2_5.4	
SF-36™ Health Status Survey	14.2_6	16.2_6.4.1
		16.2_6.4.2
		16.2_6.4.3
Concomitant Analgesic Medication Use	14.2_7.1	16.2_7.4
	14.2_7.2	
	14.2_7.3	

^a Statistical analyses tables for the ITT dataset.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

59

Analyses were performed on the ITT, evaluable, and study completers datasets using both the LOCF and OC methods; the ITT dataset was the protocol-defined primary dataset. Efficacy results are presented only for the ITT dataset. Efficacy results for the evaluable and study completers dataset were generally similar to those for the ITT dataset (Tables 14.2__8.1 through 14.2__13 and 14.2__14.1.1.1 through 14.2__18, respectively). Furthermore, results from analyses that used the OC method were generally similar to those that used the LOCF method, and differences are noted between the 2 methods.

11.4.1.1 Primary Efficacy Variable

Diary-Based Pain Rating Scale Scores at Final Evaluation

The mean improvement from baseline to final for the average diary-based Pain Rating Scale scores was statistically significantly greater for each of the ABT-594 treatment groups compared to placebo. A summary of the mean change from baseline to final for the average diary-based Pain Rating Scale scores is presented in Table 11.4a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

60

Table 11.4a Summary of the Analysis of Mean Change From Baseline^a to Final^b for the Average Diary-Based Pain Rating Scale^c Scores Using LOCF Method (Intent-to-Treat Dataset)

	Treatment Group			
	Placebo (N=58)	ABT-594		
		150 µg BID (N=56)	225 µg BID (N=58)	300 µg BID (N=53)
Baseline Visit				
Model-Based Mean (SE) ^d	6.5 (0.21)	6.6 (0.22)	6.7 (0.21)	6.7 (0.22)
Change to Final				
Model-Based Mean (SE) ^d	-1.1 (0.29)	-1.9 (0.30)*	-1.9 (0.29)*	-2.0 (0.30)*

SE = standard error.
 a Average of the last 7 pain scores prior to Day 1 of the study.
 b Average of the values from the last 7 days on study drug.
 c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
 d Least square means from 2-way ANOVA without interaction.
 * Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2 __2.1.1.1 and 14.2 __2.1.1.2 and Appendix 16.2 __6.2.1

A statistically significant linear dose response was observed for mean change from baseline to final for the average diary-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2 __2.3).

11.4.1.2 Secondary Efficacy Variables

Change From Baseline to Final

The mean improvement from baseline to final for the average site-based Pain Rating Scale scores was statistically significantly greater in each of the ABT-594 treatment groups compared to placebo.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

61

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. However, sporadic statistically significant differences were observed between placebo and 1 of the ABT-594 treatment groups for the mean change from baseline to final in the following items from the Neuropathic Pain Scale: intense, dull, and deep pain (Table 14.2 __4.1.2).

In the analysis of the mean change from baseline to final in the SF-36™ Health Status Survey, a statistically significant difference was observed between the ABT-594 225 µg BID and placebo treatment groups in the physical component summary. Subjects in the ABT-594 225 µg BID treatment group showed a greater improvement from baseline compared to subjects in the placebo treatment group. Additionally, a statistically significant difference was observed between the ABT-594 300 µg BID and placebo treatment groups in the mental component summary. Subjects in the placebo treatment group showed an improvement from baseline, while subjects in the ABT-594 300 µg BID treatment group showed a deterioration from baseline. There were no other statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the SF-36™ Health Status Survey subscales.

A summary of the mean change from baseline to final for secondary efficacy variables is presented in Table 11.4b.

McCarthy Deposition Exhibit 48

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Part 3

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

62

Table 11.4b Change from Baseline to Final for Secondary Efficacy Variables^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Site-Based Pain Rating Scale ^b Scores	(N=57)	(N=47)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	6.4 (0.25)	6.7 (0.27)	6.4 (0.30)	6.7 (0.34)
Change to Final				
Model-Based Mean (SE) ^c	-1.1 (0.36)	-2.7 (0.39)*	-2.1 (0.43)*	-2.8 (0.49)*
Neuropathic Pain Scaled Total Score	(N=57)	(N=48)	(N=40)	(N=29)
Baseline Visit				
Model-Based Mean (SE) ^c	54.3 (2.32)	54.6 (2.55)	53.5 (2.82)	56.3 (3.16)
Change to Final				
Model-Based Mean (SE) ^c	-11.4 (3.04)	-16.1 (3.34)	-15.8 (3.69)	-19.7 (4.14)
SF-36 TM Health Status Survey Physical Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	35.0 (1.29)	32.7 (1.36)	32.7 (1.28)	34.3 (1.31)
Change to Final				
Model-Based Mean (SE) ^c	0.6 (0.97)	3.2 (1.02)	3.3 (0.96)*	0.7 (0.98)
SF-36 TM Health Status Survey Mental Component ^e	(N=58)	(N=54)	(N=59)	(N=54)
Baseline Visit				
Model-Based Mean (SE) ^c	47.9 (1.50)	50.5 (1.59)	50.6 (1.49)	49.6 (1.52)
Change to Final				
Model-Based Mean (SE) ^c	1.7 (1.29)	-0.9 (1.35)	-1.3 (1.27)	-1.9 (1.30)*

NOTE: Due to the number of subjects who dropped out or failed to complete certain efficacy assessments, the number of subjects included in each of the secondary efficacy analyses was smaller than that of the primary analyses.

a Pain assessment scales are presented in Appendix 16.1.13.

b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

c Values represent model-based means (SE) which are least square means from 2-way ANOVA without interaction.

d Neuropathic pain scale (sum of 10 items): 11-Point Likert Scale (0-10), 0 = none, 10 = mos. for each of the 10 items.

e Results based on transformed scores as calculated using SF-36TM health survey manual and interpretation guide.

* Statistically significant difference versus placebo treatment group (p≤0.05).

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

63

Cross Reference: Tables 14.2__3.1.1, 14.2__4.1.1, and 14.2__6 and Appendices 16.2__6.2.2,
 16.2__6.3.1, 16.2__6.4.1, and 16.2__6.4.2

Global Impression of Change

No statistically significant differences were observed between the placebo and each of the ABT-594 treatment groups in the mean overall change from baseline in the subject and clinician global impression of change. However, each of the ABT-594 treatment groups was numerically better than placebo. A summary of the mean change from baseline to final for subject and clinician global impression of change is presented in Table 11.4c.

Table 11.4c Change from Baseline to Final for Subject and Clinician Global Impression of Change^a Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Subject Global Impression of Change ^b	(N=61)	(N=59)	(N=61)	(N=59)
Univariate Mean Change (SE) ^c	0.8 (0.18)	0.8 (0.21)	1.3 (0.21)	1.1 (0.19)
Clinician Global Impression of Change ^b	(N=61)	(N=59)	(N=60)	(N=59)
Univariate Mean Change (SE) ^c	0.7 (0.17)	0.8 (0.21)	1.2 (0.18)	1.1 (0.18)

^a Pain assessment scales are presented in Appendix 16.1.13.

^b Overall change defined as follows: 3 = much improved, 2 = moderately improved, 1 = minimally improved, 0 = no change, -1 = minimally worse, -2 = moderately worse, -3 = much worse.

^c Values represent univariate means (SE) for the Cochran-Mantel-Haenszel test.

Cross Reference: Table 14.2__5.3 and Appendix 16.2__6.5

In the distribution analyses of subject and clinician global impression of change (much, moderately, or minimally improved, no change, or much, moderately, or minimally worse) statistically significant differences from placebo were observed for the ABT-594 225 µg BID treatment group (Table 14.2__5.1). When responses were

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

64

further categorized as improved (including much, moderate, or minimal), no change, or worsened (including much, moderate, or minimal), there was a statistically significant difference between the ABT-594 225 µg BID and placebo treatment groups for clinician global impression of change. Based on the clinician's assessment, a greater proportion of subjects in the ABT-594 225 µg BID treatment group were improved (63%) compared to subjects in the placebo treatment group (42%; Table 14.2__5.2).

Dose Response

A statistically significant linear dose response was observed for mean change from baseline to final for the average site-based Pain Rating Scale scores, in the model that included the placebo treatment group (Table 14.2__3.3). No statistically significant linear dose response was observed for mean change from baseline to final for the Neuropathic Pain Scale Total Score, regardless of whether the model included or excluded the placebo treatment group (Table 14.2__4.3).

Change From Baseline to Each Week - Diary-Based Pain Rating Scale

Improvements from baseline were seen in diary-based Pain Rating Scale scores at each week for all treatment groups. In the LOCF analyses, the ABT-594 150 µg BID treatment group had statistically significantly greater mean improvements from baseline to Weeks 5, 6, and 7 for the average diary-based Pain Rating Scale scores when compared to placebo. No statistically significant differences were observed between the ABT-594 225 µg BID and placebo treatment groups at any time point. The mean improvements from baseline to Weeks 3, 4, 5, and 7 for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo. Results of OC analyses were generally similar to those of LOCF analyses, with a more consistent treatment effect observed in the OC analyses. A summary of the mean change from baseline to each week for the average diary-based Pain Rating Scale scores is presented in Table 11.4d.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

65

Table 11.4d Summary of the Analysis of Mean Change From Baseline^a to Each Week for the Average Diary-Based Pain Rating Scale^b Scores Using LOCF and OC Methods (Intent-to-Treat Dataset)

Visit	Treatment Group							
	Placebo		ABT-594					
			150 µg BID		225 µg BID		300 µg BID	
	LOCF (N=58)	OC (N=5)	LOCF (N=56)	OC (N=5)	LOCF (N=58)	OC (N=5)	LOCF (N=53)	OC (N=5)
Baseline Mean ^d	6.5	6.5 ^e	6.6	6.6	6.7	6.7	6.7	6.7
Week 1 ^d	-0.6 ^f	-0.6	-0.8	-0.8	-0.8	-0.8	-0.7	-0.7
Week 2 ^d	-1.0 ^f	-1.0	-1.1	-1.1	-1.2	-1.3	-1.4	-1.8*
Week 3 ^d	-1.0	-0.9	-1.2	-1.4	-1.5	-2.0*	-1.7*	-2.4*
Week 4 ^d	-1.1	-1.1	-1.6	-1.9*	-1.5	-2.3*	-1.9*	-2.4*
Week 5 ^d	-1.0	-1.0	-1.8*	-2.3*	-1.7	-2.5*	-1.9*	-2.9*
Week 6 ^d	-1.1	-1.1	-1.9*	-2.4*	-1.7	-2.6*	-1.8	-2.8*
Week 7 ^d	-1.1	-1.0	-1.9*	-2.4*	-1.8	-2.6*	-1.9*	-3.1*

LOCF = last observation carried forward; OC = observed cases.
Note: All values represent model-based means.

^a Average of the last 7 pain scores prior to Day 1 of the study.
^b Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.
^c No's for observed cases analyses:

	Placebo	ABT-594			
		150 µg BID	225 µg BID	300 µg BID	
Week 1	57	56	58	53	
Week 2	56	49	44	38	
Week 3	56	47	37	27	
Week 4	52	44	34	23	
Week 5	50	39	33	20	
Week 6	50	39	30	17	
Week 7	49	38	29	17	

^d Least square means from 2-way ANOVA without interaction.
^e N = 58 at baseline.
^f N = 57 at Weeks 1 and 2.
* Statistically significant difference versus placebo treatment group (p≤0.05).

Cross Reference: Tables 14.2_2.1.3 and 14.2_2.4.3 and Appendix 16.2_6.2.1

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

66

Change From Baseline to Each Visit - Diary-Based Pain Rating Scale

Each treatment group showed improvement from baseline to the 7-day average prior to each visit in diary-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits III and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID and 225 µg BID treatment groups compared to placebo. Furthermore, the mean changes from baseline to Treatment Visits II, III, and IV for the average diary-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__2.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__2.4.2).

Change From Baseline to Each Visit - Site-Based Pain Rating Scale

Each treatment group showed improvement from baseline to each visit in site-based Pain Rating Scale scores. The mean changes from baseline to Treatment Visits II, III, and IV for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 150 µg BID treatment group compared to placebo. The mean change from baseline to Treatment Visit IV for the average site-based Pain Rating Scale score was statistically significantly greater in the ABT-594 225 µg BID treatment group compared to placebo. The mean changes from baseline to each Treatment Visit for the average site-based Pain Rating Scale scores were statistically significantly greater in the ABT-594 300 µg BID treatment group compared to placebo (Table 14.2__3.1.2). Results of OC analyses were generally similar to those of LOCF analyses (Table 14.2__3.4).

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

67

11.4.1.3 Other Efficacy Variables

Proportion of Responders

The percentage of subjects having a positive response to study drug, defined as a 50% or greater improvement from baseline to the final evaluation, was analyzed for the following efficacy variables: average diary- and site-based Pain Rating Scale scores and Neuropathic Pain Scale Total Score. Comparisons between treatment groups were performed using the CMH test, with investigator as the stratification variable.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either the diary- or site-based average Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group. A summary of the proportion of subjects with a positive response to study drug as measured by average diary- and site-based Pain Rating Scale scores is presented in Table 11.4e.

Table 11.4e Proportion of Subjects Responding^a to Treatment as Measured by Diary- and Site-Based Pain Rating Scale Scores^b Using LOCF Method (Intent-to-Treat Dataset)

Variable	Treatment Group			
	Placebo	ABT-594		
		150 µg BID	225 µg BID	300 µg BID
Average Diary-Based Pain Rating Scale ^c Scores	(N=58) 12%	(N=56) 27%*	(N=58) 26%	(N=53) 26%*
Average Site-Based Pain Rating Scale ^c Scores	(N=57) 14%	(N=47) 40%*	(N=40) 35%*	(N=29) 48%*

^a Defined as a 50% or greater improvement from baseline to the final evaluation.

^b Pain assessment scales are presented in Appendix 16.1.13.

^c Pain intensity scale: 11-Point Likert Scale (0-10), 0 = no pain, 10 = worst pain possible.

* Statistically significant difference versus placebo treatment group ($p \leq 0.05$).

Cross Reference: Tables 14.2 __ 2.1.4 and 14.2 __ 3.1.3 and Appendices 16.2 __ 6.2.1 and 16.2 __ 6.2.2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

68

Concomitant Analgesic Medication Use

No statistically significant differences were observed among the treatment groups for the proportion of subjects using any analgesic medication or within 24 hours of analgesic medication at each visit during the Treatment Phase and over the entire Treatment Phase (Tables 14.2__7.1 and 14.2__7.2). There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the number of times analgesic medication was used (Table 14.2__7.3).

11.4.2 Statistical and Analytical Issues

11.4.2.1 Adjustments for Covariates

Adjustments for covariates, including sex, race, age, and weight, were not performed in the efficacy analyses.

11.4.2.2 Handling of Dropouts or Missing Data

Two sets of efficacy analyses, corresponding to the handling of missing data, were performed. The LOCF analyses used the completed pain evaluation from the previous visit for site-based pain scores and the pain evaluation from the previous days for diary data as an estimate of the missing data. Thus, in the LOCF analysis, every subject in the analysis had a value for each specified evaluation. This technique was intended to reduce bias caused by subjects who prematurely discontinued due to lack of efficacy. The OC method did not estimate missing evaluations and a subject who did not have a pain evaluation on a scheduled visit was excluded from the OC analysis for that visit. Results obtained with the OC method were generally consistent with those obtained with the LOCF method.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analyses were performed.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

69

11.4.2.4 Multicenter Studies

This was a multicenter study. The treatment-by-center interaction was not statistically significant at an $\alpha=0.10$ in the analysis of change from baseline to the final evaluation for the diary-based Pain Rating Scale scores (Table 14.2__2.2), indicating homogeneity of treatment effects across centers for the primary endpoint. Therefore, the treatment-by-center interaction term was not used in the primary or secondary analyses. Additionally, since the treatment-by-center interaction term was not used in the primary analysis, data from study centers with less than 1 subject per treatment group in the ITT dataset, were not combined for the analyses.

11.4.2.5 Multiple Comparisons/Multiplicity

No statistical adjustments were made for multiple comparisons.

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Subjects who received less than 7 days of study drug or who had no baseline or post Day 7 pain assessment for the diary-based Pain Rating Scale were identified prior to breaking the blind and were excluded from the evaluable dataset. Results for ITT and evaluable datasets were similar.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

The study was not designed to assess equivalence to an active control.

11.4.2.8 Examination of Subgroups

Subgroup analyses for potentially influential factors were not performed.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

70

11.4.3 Tabulation of Individual Response Data

There were no tabulations of individual response to study drug except as provided in the data listings (Appendix 16.2).

11.4.4 Drug Dose, Drug Concentration, and Relationship to Response

Blood samples for ABT-594 plasma assay were to be collected for all subjects at Treatment Visits I and IV. For those subjects participating in the pharmacokinetic sampling for pharmacokinetic profile (approximately 30 subjects), additional blood samples were collected at Treatment Visits I and IV. Plasma concentrations of ABT-594 are listed for each subject in Appendix 16.2__5.3.1.

A complete discussion of the pharmacokinetic variables analyzed will be presented in a separate Clinical Pharmacokinetic Report.

11.4.5 Drug-Drug and Drug-Disease Interactions

Analyses which examined drug-drug and drug-disease interactions were not performed.

11.4.6 By-Subject Displays

There were no by-subject displays of individual response to study drug except as provided in the data listings (Appendix 16.2).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

71

11.4.7 Efficacy Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to the subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

11.5 Pharmacokinetic Variables

Complete pharmacokinetic results will be presented in a separate Clinical Pharmacokinetic Report.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

72

12.0 Safety Evaluation

All 266 randomized subjects who were treated with study drug (65 placebo, 65 ABT-594 150 µg, 69 ABT-594 225 µg, and 67 ABT-594 300 µg BID) were evaluated for safety. Adverse events, clinical laboratory data, vital signs (including weight), and 12-lead ECG data were used to evaluate safety.

12.1 Extent of Exposure

The mean duration of treatment was statistically significantly different among treatment groups. The placebo treatment group received study drug for a mean 44.3 days, as compared to 35.9, 28.6, and 22.7 days for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups, respectively. A summary of the extent of exposure to study drug is presented in Table 12.1a.

Table 12.1a Extent of Exposure

Duration of Treatment (Days)	Treatment Group n (%)			
	Placebo (N=65)	ABT-594		
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
<7	1 (2%)	8 (12%)	14 (20%)	12 (18%)
7 - 13	2 (3%)	5 (8%)	14 (20%)	19 (28%)
14 - 20	4 (6%)	4 (6%)	4 (6%)	6 (9%)
21 - 27	5 (8%)	6 (9%)	3 (4%)	8 (12%)
28 - 34	0	2 (3%)	0	3 (4%)
35 - 41	1 (2%)	0	4 (6%)	2 (3%)
42 - 48	3 (5%)	5 (8%)	3 (4%)	1 (1%)
≥49	49 (75%)	35 (54%)	27 (39%)	16 (24%)
Mean (SD)*	44.3 (13.5)	35.9 (19.1)	28.6 (20.5)	22.7 (18.0)
Note: Percentages may not sum to 100 due to rounding. SD = standard deviation.				
* Statistically significant difference among treatment groups (p≤0.05).				

Cross Reference: Table 14.1__8 and Appendix 16.2__5.1.1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

73

12.2 Adverse Events

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Adverse Events		16.2_7.1.1
All Treatment-Emergent	14.3.1_1.1	
by Severity	14.3.1_1.2.1	
	14.3.1_1.2.2	
by Relationship to Study Drug	14.3.1_1.3.1	
	14.3.1_1.3.2	
Incidence Across Time	14.3.1_2.1	
Prevalence Across Time	14.3.1_2.2	
Identification of Subjects	14.3.1_3.1	
Medical Terms and Descriptions Associated with Each COSTART Term	14.3.1_3.2	

12.2.1 Brief Summary of Adverse Events

Among all treated subjects, 66% of subjects who received placebo and 83%, 90%, and 91% of subjects who received ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%,

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

74

respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, vomiting, dizziness, abnormal dreams, and headache.

12.2.2 Display of Adverse Events

A summary of the treatment-emergent adverse events occurring in ≥10% of subjects in any ABT-594 treatment group is presented by the investigator's assessment of relationship to study drug in Table 12.2a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

76

Most adverse events in all treatment groups were mild or moderate in severity and were considered by the investigator to be possibly or probably related to study drug (Tables 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, and 14.3.1__1.3.2).

12.2.3 Analysis of Adverse Events

The overall incidence of treatment-emergent adverse events was statistically significantly higher for subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (83%, 90%, and 91%, respectively) than for subjects in the placebo treatment group (66%). Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg BID and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). No other statistically significant treatment differences were observed for any specific treatment-emergent adverse event (Table 14.3.1__1.1).

Five percent (3/65) of placebo-treated subjects, 11% (7/65) of ABT-594 150 µg-treated subjects, 12% (8/69) of ABT-594 225 µg-treated subjects, and 12% (8/67) of ABT-594 300 µg BID-treated subjects experienced at least 1 severe adverse event, most of which were considered probably related to study drug by the investigator. The remaining adverse events were mild or moderate in severity. A summary of the severity of treatment-emergent adverse events grouped by body system and COSTART term is presented in Tables 14.3.1__1.2.1 and 14.3.1__1.2.2.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

77

12.2.4 Listing of Adverse Events by Subject

The location of adverse event data is presented below.

Assessment	Statistical Analyses Tables	Individual Subject Listing Appendix
Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description With Subject Number Identification (All Treated Subjects)	14.3.1__3.1	16.2__7.1.1
Adverse Event Medical Terms and Descriptions	14.3.1__3.2	

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The location of deaths, other serious adverse events, and other significant adverse event data is presented below.

Assessment	Statistical Analyses Tables	Narrative Section	Individual Subject Listing Appendix
Deaths	14.3.2__1.1	14.3.3	16.2__7.2
Serious Adverse Events	14.3.2__1.2	14.3.3	16.2__7.1.2
Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued	14.3.2__2	14.3.3	16.2__7.1.1
Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Discontinued Grouped by Body System and COSTART Term	14.3.2__3		16.2__7.1.1

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

73

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1 Deaths

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug.

A listing of subjects who died during the course of the study is presented in Appendix 16.2__7.2.

12.3.1.2 Other Serious Adverse Events

In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported a serious adverse event during the study (Table 14.3.2__1.2). One of these subjects reported an event (palpitation reported in an ABT-594 300 µg BID-treated subject) considered probably related to study drug. The event was a single occurrence and resolved within 90 minutes. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

Eight subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each of these subjects had multiple risk factors for cardiovascular disease. Subjects reporting serious adverse events (including death) during the study are presented in Table 12.3a.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

79

Table 12.3a Subjects Reporting Serious Adverse Events During the Study

Treatment Group	Investigator/ Subject	Age (yrs)/ Sex	Day of Onset ^a	Day of Resolution ^a	COSTART Term - Reason Serious ^b	Relationship to Study Drug
Placebo	DeBolt/4053	52/F	52 (2)	53 (3)	Gastroenteritis - HO	Not related
			52 (2)	53 (3)	Dehydration - HO	Not related
			52 (2)	53 (3)	Ketosis - HO	Not related
	Singer/4401	53/M	34 49 (9)	42 (1) unknown	Angina Pectoris ^c - HO Atrial Fibrillation - HO	Not related Not related
	Weinstein/4027	65/F	9 (1)	12 (4)	Cerebrovascular Accident ^c - HO	Probably not
ABT-594 150 µg BID	Baume/4149	71/M	65 (15) 65 (15)	66 (16) 66 (16)	Angina Pectoris - HO Myocardial Infarct - HO	Not related Not related
			15 (1) 15 (1)	17 (3) ^d 22 (3) ^d	Syncope ^c - HO Atrial Fibrillation ^c - HO	Not related Not related
	Kipnes/4070	48/F	10	12	Pain ^c - HO	Not related
	Singer/4412	57/M	36	50	Peripheral Vascular Disorder - HO	Not related
	Storey/4100 ^e	56/F	79 (58) ^f	79 (58)	Suicide Attempt - DEA	Not related
	Kluge/4133	66/M	6	9	Gastrointestinal Disorder ^c - HO	Not related
	Shaibani/4451	60/F	18 18	18 20 (2)	Dyspnea ^c - HO Angina Pectoris ^c - HO	Probably not Probably not
ABT-594 300 µg BID	Drucker/4002	70/M	4	4	Palpitation ^c - HO	Probably
	Holmlund/4193 ^e	55/M	40 (32) ^f	64 (56)	Accidental Injury ^g - HO	Not related
	Holmlund/4197	62/F	5	6 (1)	Angina Pectoris ^c - HO	Not related
	Weinstein/4031	80/M	43 (7)	80 (44) ^d	Cellulitis ^c - HO	Not related

M = male, F = female.
^a Number in parentheses represents the number of days after the last dose of study drug.
^b HO=hospitalization; DEA=death.
^c Adverse event leading to premature discontinuation.
^d Adverse event was ongoing as of this day.
^e Subject prematurely discontinued due to another adverse event.
^f Adverse event onset >30 days after the last dose of study drug.
^g Described as status post fall down stairs.

Cross Reference: Table 14.3.2 __ 1.2 and Appendices 16.2 __ 7.1.1 and 16.2 __ 7.1.2

A listing of all subjects who experienced serious adverse events during the study is presented by treatment group and subject number in Table 14.3.2 __ 1.2.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

80

12.3.1.3 Other Significant Adverse Events

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) *prematurely discontinued study drug due to 1 or more adverse events*. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

A summary of adverse events leading to premature discontinuation of study drug is presented by treatment group in Table 12.3b.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

81

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects)

COSTART Term	Treatment Group n (%)			
	Placebo (N=65)	ABT-594		
		150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Any Event*	6 (9%)	18 (28%)*	32 (46%)*	44 (66%)*
Nausea	1 (2%)	8 (12%)*	15 (22%)*	20 (30%)*
Dizziness	0	4 (6%)	11 (16%)*	13 (19%)*
Vomiting	0	4 (6%)	10 (14%)*	12 (18%)*
Abnormal Dreams	0	3 (5%)	6 (9%)*	7 (10%)*
Headache	0	1 (2%)	3 (4%)	8 (12%)*
Insomnia	0	1 (2%)	5 (7%)	4 (6%)
Asthenia	0	0	3 (4%)	6 (9%)*
Dyspepsia	0	2 (3%)	4 (6%)	3 (4%)
Diarrhea	0	0	4 (6%)	2 (3%)
Pain	0	1 (2%)	1 (1%)	4 (6%)
Sweating	0	1 (2%)	2 (3%)	2 (3%)
Chills	0	0	2 (3%)	2 (3%)
Flatulence	1 (2%)	0	1 (1%)	2 (3%)
Hypertension	0	0	2 (3%)	2 (3%)
Nervousness	0	0	3 (4%)	1 (1%)
Abdominal Pain	0	0	1 (1%)	2 (3%)
Angina Pectoris	1 (2%)	0	1 (1%)	1 (1%)
Chest Pain	0	0	1 (1%)	2 (3%)
Dyspnea	0	0	1 (1%)	2 (3%)
Palpitation	0	0	1 (1%)	2 (3%)
Taste Perversion	0	2 (3%)	0	1 (1%)
Abnormal Gait	0	0	2 (3%)	0
Accidental Injury	1 (2%)	0	0	1 (1%)
Amblyopia	0	1 (2%)	1 (1%)	0
Anorexia	0	0	1 (1%)	1 (1%)
Confusion	0	0	1 (1%)	1 (1%)
Hallucinations	0	0	2 (3%)	0
Malaise	0	0	1 (1%)	1 (1%)
Paresthesia	0	0	1 (1%)	1 (1%)
Tachycardia	0	0	1 (1%)	1 (1%)
Thinking Abnormal	0	0	0	2 (3%)
Abdomen Enlarged	0	0	0	1 (1%)
Abnormal Vision	0	0	0	1 (1%)
Alopecia	0	0	1 (1%)	0
Anxiety	0	0	1 (1%)	0
Arthralgia	0	0	1 (1%)	0
Ataxia	0	0	1 (1%)	0
Atrial Fibrillation	0	1 (2%)	0	0
Back Pain	0	0	0	1 (1%)

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ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

82

- a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.
* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Table 12.3b Treatment-Emergent Adverse Events Leading to Premature Discontinuation of Study Drug (All Treated Subjects; continued)

COSTART Term	Treatment Group n (%)			
	Placebo (N=65)	150 µg BID (N=65)	225 µg BID (N=69)	300 µg BID (N=67)
Cellulitis	0	0	0	1 (1%)
Cerebrovascular Accident	1 (2%)	0	0	0
Depersonalization	1 (2%)	0	0	0
Depression	0	0	0	1 (1%)
Dry Mouth	0	0	0	1 (1%)
Emotional Lability	0	0	1 (1%)	0
Erecta	0	0	0	1 (1%)
Eye Disorder	0	0	1 (1%)	0
Flu Syndrome	0	0	0	1 (1%)
Gastroenteritis	1 (2%)	0	0	0
Gastrointestinal Disorder	0	0	1 (1%)	0
Glossitis	0	1 (2%)	0	0
Hyperglycemia	0	0	0	1 (1%)
Infection	1 (2%)	0	0	0
Leg Cramps	0	0	0	1 (1%)
Rash	0	0	0	1 (1%)
Rectal Hemorrhage	0	0	0	1 (1%)
Somnolence	0	1 (2%)	0	0
Stupor	0	0	0	1 (1%)
Syncope	0	1 (2%)	0	0
Tremor	0	0	1 (1%)	0
Vasodilatation	0	0	0	1 (1%)

a Subjects may have reported more than 1 adverse event leading to premature discontinuation, but were counted only once in the total.
* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.2_3 and Appendix 16.2_7.1.1

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

83

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Narratives for subjects who died, reported a serious adverse event, or prematurely discontinued from the study at least in part to an adverse event are presented in Section 14.3.3.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase (Table 14.3.2__1.1). Subject 4100 died on Day 79 due to a suicide attempt (COSTART term: suicide attempt) that the investigator considered to be unrelated to study drug.

Thirteen subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) reported 1 or more serious adverse events other than death. However, only 1 of these subjects (ABT-594 300 µg BID) reported an event considered to be probably related to study drug. This subject had a single episode of palpitation (COSTART term: palpitation) on Day 4 that resolved without further incident within 90 minutes. The remaining events were all considered to be not related or probably not related to study drug. Another 1 of the 13 subjects (ABT-594 300 µg BID) reported a serious adverse event (COSTART term: accidental injury [described as "status post fall down stairs"]) with onset >30 days after the last dose of study drug.

One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The overall incidence of subjects prematurely discontinuing due to adverse events was statistically significantly higher for the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups (28%, 46%, and 66%, respectively) than for the placebo treatment group (9%). Statistically significantly higher proportions of subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups prematurely discontinued study drug due to nausea (12%, 22%, and 30%, respectively) compared to subjects in the placebo treatment group (2%). Statistically significantly higher proportions of subjects in the ABT-594 225 µg and 300 µg BID treatment groups prematurely discontinued study drug

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

84

due to dizziness (16% and 19%, respectively), vomiting (14% and 19%, respectively), and abnormal dreams (9% and 10%, respectively) compared to subjects in the placebo treatment group (0% each). A statistically significantly higher proportion of subjects in the ABT-594 300 µg BID treatment group prematurely discontinued study drug due to headache (12%) compared to subjects in the placebo treatment group (0%).

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

The location of clinical laboratory data is presented below.

Laboratory Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing ^a Appendix
Hematology	14.3.4_1.1	14.3.4_3.1	16.2_8.2.1
	14.3.4_2.1	14.3.4_4.1	16.2_8.2.2
			16.2_8.2.3
			16.2_8.2.4
			16.2_8.2.5
Blood Chemistry	14.3.4_1.2	14.3.4_3.2	16.2_8.3.1
	14.3.4_2.2	14.3.4_4.2	16.2_8.3.2
			16.2_8.3.3
			16.2_8.3.4
			16.2_8.3.5
Urinalysis	14.3.4_1.3	14.3.4_3.3	16.2_8.4.1
	14.3.4_2.3	14.3.4_4.3	16.2_8.4.2
			16.2_8.4.3
			16.2_8.4.4
			16.2_8.4.5

^a Baseline determinations are also presented in Appendix 16.2_4.

Laboratory normal reference ranges are presented in Appendix 16.2_8.1. Criteria for potentially clinically significant laboratory values (i.e., very high or very low values) are presented in Table 14.3.4_1.0.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

85

12.4.2 Evaluation of Each Laboratory Parameter

12.4.2.1 Laboratory Values Over Time

Hematology

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for hematology parameters is presented in Table 12.4a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

86

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters

Hematology Parameter (units)	Treatment Group			
	Placebo (N=62)	150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Hemoglobin (g/dL)				
Baseline Mean	14.10	13.80	13.81	14.02
Mean Change to Minimum	-0.46	-0.30	-0.21*	-0.09*
Hematocrit (%)				
Baseline Mean	40.95	40.39	40.11	40.82
Mean Change to Minimum	-1.06	-1.16	-0.79	-0.26*
Mean Change to Maximum	1.60	0.87	0.73*	0.90
RBC Count (x 10 ¹² /L)				
Baseline Mean	4.66	4.61	4.58	4.70
Mean Change to Minimum	-0.13	-0.11	-0.05*	-0.05*
MCV (fL)				
Baseline Mean	88.24	87.79	87.65	87.26
Mean Change to Maximum	2.00	1.26	0.68*	1.24
MCH (pg)				
Baseline Mean	30.52	30.07	30.21	30.00
Mean Change to Minimum	-0.73	-0.30	-0.33*	-0.27*
Mean Change to Final	-0.29	0.16*	-0.08	0.00
MCHC (g/dL)				
Baseline Mean	34.50	34.30	34.45	34.47
Mean Change to Minimum	-1.08	-0.46*	-0.47*	-0.52*
Platelet Count (x 10 ⁹ /L)				
Baseline Mean	246.70	250.27	253.70	241.32
Mean Change to Minimum	-10.98	-13.27	-7.82	4.05*
Mean Change to Maximum	29.33	14.15*	10.89*	26.84
WBC Count (x 10 ⁹ /L)				
Baseline Mean	8.01	7.60	7.36	6.95
Mean Change to Minimum	-0.51	-0.50	-0.03*	0.02*

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ABBT238679

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

87

Neutrophils (%)				
Baseline Mean	61.01	62.82	61.86	50.62
Mean Change to Minimum	-2.25	-2.39	-0.60	0.09*
Lymphocytes (%)				
Baseline Mean	30.04	28.78	29.70	30.53
Mean Change to Maximum	2.08	2.17	0.63	0.02*
Eosinophils (%)				
Baseline Mean	2.90	2.32	2.38	2.53
Mean Change to Minimum	-0.82	-0.50	-0.34*	-0.60
Mean Change to Maximum	0.41	0.32	0.29	-0.05*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Table 12.4a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Hematology Parameters (continued)

Hematology Parameter (units)	Treatment Group			
	Placebo (N=60)	ABT-594		
		150 µg BID (N=59)	225 µg BID (N=65)	300 µg BID (N=61)
Prothrombin Time (sec)				
Baseline Mean	12.30	12.33	12.20	12.79
Mean Change to Maximum	0.39	0.15	0.08*	0.25
Activated Partial Thromboplastin Time (sec)				
Baseline Mean	24.32	24.69	25.11	25.53
Mean Change to Maximum	1.60	0.72	0.57*	0.27*
Mean Change to Final	0.56	-0.13	-0.24	-0.53*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Blood Chemistry

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

88

change from baseline to minimum, maximum, and/or final value for blood chemistry parameters is presented in Table 12.4b.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

89

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Glucose (mg/dL)				
Baseline Mean	175.68	192.13	169.09	183.90
Mean Change to Maximum	57.79	44.36	39.39	7.94*
Total Protein (g/dL)				
Baseline Mean	7.25	7.24	7.31	7.26
Mean Change to Maximum	0.19	0.14	0.03*	0.13
Mean Change to Final	0.03	-0.06	-0.13*	0.00
Total Bilirubin (mg/dL)				
Baseline Mean	0.40	0.43	0.38	0.36
Mean Change to Minimum	-0.05	-0.07	-0.04	-0.00*
Alkaline Phosphatase (IU/L)				
Baseline Mean	75.94	78.74	81.88	74.35
Mean Change to Maximum	4.27	1.43	-0.14*	1.95
SGOT/AST (IU/L)				
Baseline Mean	22.35	21.87	23.70	22.81
Mean Change to Maximum	2.76	1.56	-1.32*	0.84
SGPT/ALT (IU/L)				
Baseline Mean	23.08	24.11	24.65	26.42
Mean Change to Maximum	3.69	0.79	-1.44*	0.08
Sodium (mEq/L)				
Baseline Mean	141.18	139.82	140.85	140.16
Mean Change to Minimum	-2.77	-1.59	-1.92	-0.87*
Potassium (mEq/L)				
Baseline Mean	4.55	4.41	4.53	4.38
Mean Change to Minimum	-0.32	-0.15*	-0.19	-0.15*
Chloride (mEq/L)				
Baseline Mean	104.37	102.56	103.32	102.23
Mean Change to Minimum	-3.00	-1.15*	-1.95	-1.34*
Mean Change to Final	-0.71	0.80*	-1.00	0.29
Bicarbonate (mEq/L)				
Baseline Mean	26.42	26.72	27.10	27.57
Mean Change to Maximum	1.26	0.33*	0.71	0.61
Calcium (mg/dL)				
Baseline Mean	9.51	9.46	9.57	9.51
Mean Change to Minimum	-0.33	-0.17*	-0.21	-0.07*
Inorganic Phosphorus (mg/dL)				
Baseline Mean	3.64	3.71	3.72	3.56
Mean Change to Minimum	-0.42	-0.27	-0.11*	-0.11*

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

90

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Table 12.4b Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Blood Chemistry Parameters (continued)

Blood Chemistry Parameter (units)	Treatment Group			
	Placebo (N=62)	ABT-594		
		150 µg BID (N=61)	225 µg BID (N=66)	300 µg BID (N=62)
Cholesterol (mg/dL)				
Baseline Mean	190.44	199.54	204.95	203.79
Mean Change to	12.71	4.44*	-1.05*	0.21*
Maximum	1.27	-3.66	-8.55*	-5.53
Mean Change to Final				
Triglycerides (mg/dL)				
Baseline Mean	239.31	274.03	277.55	300.03
Mean Change to	80.69	42.26	28.77*	-7.34*
Maximum	39.32	-9.11*	-3.59	-36.23*
Mean Change to Final				

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4_1.2 and Appendices 16.2_8.3.1 through 16.2_8.3.5

Urinalysis

Sporadic statistically significant differences were observed between placebo and each of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for urinalysis is presented in Table 12.4c.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

91

Table 12.4c Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Urinalysis Parameters

Urinalysis Parameter (units)	Treatment Group			
	Placebo (N=61)	150 µg BID (N=58)	225 µg BID (N=65)	300 µg BID (N=62)
Urine pH				
Baseline Mean	5.75	5.59	5.51	5.68
Mean Change to Minimum	-0.67	-0.36*	-0.26*	-0.19*
Mean Change to Final	-0.34	-0.12	-0.09	0.00*
Specific Gravity				
Baseline Mean	1.02	1.02	1.02	1.02
Mean Change to Minimum	-0.004	-0.003	-0.002	-0.001*

* Statistically significant difference versus the placebo treatment group ($p \leq 0.05$).

Cross Reference: Table 14.3.4__1.3 and Appendices 16.2__8.4.1 through 16.2__8.4.4

12.4.2.2 Individual Subject Changes

The percentage of subjects with shifts in laboratory parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.4__2.1 for hematology variables, Table 14.3.4__2.2 for blood chemistry variables, and Table 14.3.4__2.3 for urinalysis variables. The majority of subjects had clinical laboratory values within normal range at the Baseline and Final Visits.

12.4.2.3 Individual Clinically Significant Abnormalities

Hematology Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant hematology values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.1. The percentages of subjects who had hematology values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed hematology

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

92

values that met the potentially clinically significant criteria are presented in Table 12.4d; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4d Number and Percentage of Subjects with Hematology Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Hemoglobin	High: ≥ 18.5 g/dL (males)	(N=54) 1 (2%)	(N=50) 0	(N=45) 0	(N=34) 0
	≥ 16.5 g/dL (females)				
Hematocrit	Low: $\leq 37\%$ (males)	(N=49) 4 (8%)	(N=47) 3 (6%)	(N=42) 4 (10%)	(N=32) 0
	$\leq 32\%$ (females)				
RBC	Low: $\leq 3.8 \times 10^{12}/L$ (males)	(N=53) 0	(N=50) 0	(N=45) 1 (2%)	(N=34) 0
	$\leq 3.5 \times 10^{12}/L$ (females)				
WBC	High: $\geq 16.0 \times 10^9/L$	(N=56) 0	(N=51) 0	(N=45) 0	(N=34) 1 (3%)

Cross Reference: Table 14.3.4__4.1 and Appendices 16.2__8.2.1 through 16.2__8.2.5

Individual subjects with hematology values that met the potentially clinically significant criteria are presented in Table 14.3.4__3.1.

Blood Chemistry Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant blood chemistry values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4__4.2. The percentages of subjects who had blood chemistry values that met the potentially clinically significant criteria were generally similar among the treatment groups. One subject (4246) in the ABT-594 300 µg BID treatment group had a very high glucose on Day 14 (334 mg/dL) and was prematurely discontinued from study drug due to hyperglycemia. However, the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

93

subject's glucose was high (229 mg/dL) at baseline, indicating poor control of her diabetes. The percentages of subjects who developed blood chemistry values that met the potentially clinically significant criteria are presented in Table 12.4e; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4e Number and Percentage of Subjects with Blood Chemistry Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Glucose	High: ≥ 175 mg/dL	(N=33) 19 (58%)	(N=23) 16 (70%)	(N=28) 16 (57%)	(N=20) 7 (35%)
	Low: ≤ 45 mg/dL	0	1 (4%)	0	0
Uric Acid	High: ≥ 10.5 mg/dL (males)	(N=56) 0	(N=51) 0	(N=42) 0	(N=34) 1 (3%)
	≥ 8.5 mg/dL (females)				
BUN	High: ≥ 30 mg/dL	(N=56) 2 (4%)	(N=51) 1 (2%)	(N=43) 0	(N=34) 1 (3%)
Creatinine	High: ≥ 2.0 mg/dL	(N=57) 0	(N=51) 1 (2%)	(N=45) 0	(N=35) 0
Chloride	Low: ≤ 90 mEq/L	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Calcium	Low: ≤ 8.2 mg/dL	(N=57) 1 (2%)	(N=51) 0	(N=45) 0	(N=35) 0
Triglycerides	High: ≥ 600 mg/dL	(N=54) 2 (4%)	(N=43) 0	(N=40) 2 (5%)	(N=34) 1 (3%)

Cross Reference: Table 14.3.4 __ 4.2 and Appendices 16.2 __ 8.3.1 through 16.2 __ 8.3.5

Individual subjects with blood chemistry values that met the potentially clinically significant criteria are presented in Table 14.3.4 __ 3.2.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

94

Urinalysis Values Meeting Criteria for Potentially Clinically Significant Values

Criteria for potentially clinically significant urinalysis values are presented in Table 14.3.4 __1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.4 __4.3. The percentages of subjects who had urinalysis values that met the potentially clinically significant criteria were generally similar among the treatment groups. None of these values were associated with premature discontinuations. The percentages of subjects who developed urinalysis values that met the potentially clinically significant criteria are presented in Table 12.4f; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

Table 12.4f Number and Percentage of Subjects with Urinalysis Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
Urine Glucose	High: ≥3+ ^a	(N=50) 12 (24%)	(N=44) 12 (27%)	(N=41) 10 (24%)	(N=27) 5 (19%)
Urine Protein	High: ≥3+ ^a / ≥10	(N=56) 0	(N=50) 0	(N=45) 0	(N=32) 1 (3%)
Urine Ketones	High: ≥3+ ^a	(N=57) 1 (2%)	(N=50) 0	(N=45) 0	(N=32) 0
Urine RBCs	High: ≥8/hpf (male) ≥10/hpf (female)	(N=57) 2 (4%)	(N=50) 3 (6%)	(N=44) 0	(N=31) 2 (6%)
Urine WBCs	High: ≥10/hpf ≥ 2+	(N=55) 4 (7%)	(N=50) 2 (4%)	(N=45) 3 (7%)	(N=32) 4 (13%)

hpf = high power field.

^a ≥3+ on a scale with 4+ being the maximum value.

Cross Reference: Table 14.3.4 __4.3 and Appendices 16.2 __8.4.1 through 16.2 __8.4.4

Individual subjects with urinalysis values that met the potentially clinically significant criteria are presented in Table 14.3.4 __3.3.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

95

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Listing of Individual Measurements by Subject and Each Abnormal Value

The location of vital sign, physical findings, and safety data is presented below.

Assessment	Statistical Analyses Tables	Values of Potential Clinical Significance	Individual Subject Listing Appendix
Physical Examination	None	None	16.2__4.4
Vital Signs	14.3.5__1	14.3.5__2 14.3.5__3	16.2__9.1
ECGs	14.3.6__1 14.3.6__2	14.3.6__3 14.3.6__4	16.2__9.2

No normal reference range was used for evaluating vital sign or ECG variables. Criteria for potentially clinically significant values (i.e., Very High or Very Low values) for vital signs and ECG are presented in Table 14.3.4__1.0.

12.5.2 Findings on Physical Examination

Clinically significant deteriorations from baseline physical examination were captured as adverse events (Appendices 16.2__4.4 and 16.2__7.1.1).

12.5.3 Vital Signs Evaluation

12.5.3.1 Vital Signs Values Over Time

Statistically significant differences were observed between treatment groups for mean change from baseline to minimum and/or maximum; however, none of the mean differences was considered clinically meaningful. A summary of statistically significant treatment group differences in mean change from baseline to minimum, maximum, and/or final value for vital sign parameters is presented in Table 12.5a.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

96

Table 12.5a Statistically Significant Treatment Group Differences in Mean Change From Baseline to Minimum, Maximum, and/or Final Value - Vital Sign Parameters

Vital Sign Parameter (units)	Treatment Group			
	Placebo (N=62)	150 µg BID (N=62)	225 µg BID (N=66)	300 µg BID (N=64)
Systolic Blood Pressure (mm Hg)				
Baseline Mean	130.8	134.3	136.8	133.9
Mean Change to Maximum	11.8	8.6	3.9*	7.6
Diastolic Blood Pressure (mm Hg)				
Baseline Mean	76.3	78.7	77.6	76.5
Mean Change to Maximum	6.4	4.5	2.7*	4.6
Mean Change to Final	1.4	-3.2*	-1.5	0.8
Heart Rate (bpm)	(N=62)	(N=61)	(N=66)	(N=63)
Baseline Mean	76.1	75.4	75.2	76.1
Mean Change to Final	2.5	-1.8*	2.0	0.6
Weight (pounds)	(N=61)	(N=60)	(N=62)	(N=60)
Baseline Mean	204.0	199.8	199.1	204.1
Mean Change to Minimum	-0.1	-2.1*	-1.9*	-2.8*
Mean Change to Maximum	1.8	0.0*	-0.1*	-1.4*
Mean Change to Final	1.1	-0.8*	-1.0*	-2.0*

* Statistically significant difference versus the placebo treatment group (p≤0.05).

Cross Reference: Table 14.3.5__1 and Appendix 16.2__9.1

12.5.3.2 Individual Subject Changes

Criteria for potentially clinically significant vital signs and weight values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.5__3. The percentages of subjects who had vital signs values that met the potentially clinically significant criteria were generally similar among the treatment groups. A very high sitting systolic blood pressure value was reported by 0 placebo-treated subjects, 6% (3/50) of ABT-594 150 µg-treated subjects, 0 ABT-594 225 µg-treated subjects, and 3% (1/36) of ABT-594 300 µg BID-treated subjects (Table 14.3.5__3).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

97

12.5.4 Electrocardiogram Evaluation

12.5.4.1 ECG Values Over Time

No statistically significant differences were observed between placebo and any of the other treatment groups for mean change from baseline to minimum, maximum, and/or final value for ECG variables (Table 14.3.6__1).

12.5.4.2 Individual Clinically Significant Abnormalities

The percentage of subjects with shifts in ECG parameters from baseline to the final value using potentially clinically significant criteria to define categories are presented in Table 14.3.6__2. The majority of subjects had ECG values within normal range at the Baseline and Final Visits.

12.5.4.3 Individual Clinically Significant Abnormalities

Criteria for potentially clinically significant ECG values are presented in Table 14.3.4__1.0, and a summary of the percentages of subjects with values meeting these criteria is presented in Table 14.3.6__4. The percentages of subjects who had ECG values that met the potentially clinically significant criteria were generally similar among the treatment groups. Of note, the high QT_C interval in an ABT-594 225 µg BID-treated subject (4081) was an isolated occurrence that was not associated with an adverse event. The percentages of subjects who developed ECG values that met the potentially clinically significant criteria are presented in Table 12.5b; only those parameters that had at least 1 subject who met the potentially clinically significant criteria are presented.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

98

Table 12.5b Number and Percentage of Subjects with ECG Values Meeting Potentially Clinically Significant Criteria (All Treated Subjects)

Variable	Criteria	Treatment Group n (%)			
		Placebo	ABT-594		
			150 µg BID	225 µg BID	300 µg BID
QT _c Interval ^a		(N=49)	(N=41)	(N=30)	(N=21)
	High: ≥500 msec	0	0	1 (3%)	0
PR Interval		(N=44)	(N=41)	(N=30)	(N=20)
	High: ≥210 msec	1 (2%)	0	1 (3%)	0
Heart Rate		(N=50)	(N=41)	(N=31)	(N=21)
	High: ≥120 bpm and increased ≥30 bpm from baseline	0	0	2 (6%)	0

^a QT_c calculated as QT divided by the square root of RR interval.

Cross Reference: Table 14.3.6__4 and Appendix 16.2__9.2

Individual subjects with ECG values that met the potentially clinically significant criteria are summarized in Table 14.3.6__3.

12.6 Safety Conclusions

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

99

BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

100

13.0 Discussion and Overall Conclusions

ABT-594 at 150 µg, 225 µg, and 300 µg BID was statistically significantly superior to placebo for the primary efficacy variable, the mean change from baseline to final for the average diary-based Pain Rating Scale. Furthermore, the mean improvement from baseline to final for the average site-based Pain Rating Scale score was statistically significantly superior in each of the ABT-594 treatment groups compared to placebo. Statistically significant linear dose responses were observed in the model that included the placebo treatment group for mean change from baseline to final for the average diary- and site-based Pain Rating Scale scores.

A statistically significantly greater proportion of subjects in all of the ABT-594 treatment groups had at least a 50% improvement in either their average diary- or site-based Pain Rating Scale scores at the final evaluation compared to subjects in the placebo treatment group.

There were no statistically significant differences between the placebo treatment group and any of the ABT-594 treatment groups for the mean change from baseline to final in the Neuropathic Pain Scale Total score. In the analysis of the mean change from baseline to final in SF-36™ Health Status Survey, a statistically significant improvement was observed for the ABT-594 225 µg BID treatment group in the physical component summary compared to the placebo treatment group. However, statistically significant worsening was observed for the ABT-594 300 µg BID treatment group in the mental component summary compared to the placebo treatment group.

Among all treated subjects, 66% of subjects receiving placebo and 83%, 90%, and 91% of subjects receiving ABT-594 150 µg, 225 µg, and 300 µg BID, respectively, reported treatment-emergent adverse events. The overall incidence of adverse events was statistically significantly higher for each of the ABT-594 treatment groups than for the placebo treatment group. The most frequently reported (≥10% of subjects in any ABT-594 treatment group) treatment-emergent adverse events were nausea, dizziness, vomiting, abnormal dreams, headache, asthenia, diarrhea, dyspepsia, and insomnia.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

101

Subjects in the ABT-594 150 µg, 225 µg, and 300 µg BID treatment groups had statistically significantly higher incidences of treatment-emergent nausea (34%, 43%, and 46%, respectively), vomiting (15%, 25%, and 21%, respectively), abnormal dreams (22%, 22%, and 18%, respectively), and dizziness (17%, 35%, and 30%, respectively) compared to subjects in the placebo treatment group (11%, 3%, 0%, and 5%, respectively). A statistically significantly greater proportion of subjects in the ABT-594 225 µg and 300 µg BID treatment groups reported treatment-emergent asthenia (16% and 21%, respectively) compared to subjects in the placebo treatment group (2%). Subjects in the placebo treatment group had a statistically significantly greater incidence of treatment-emergent infection (15%) compared to subjects in the ABT-594 300 µg BID treatment group (3%). Most adverse events were mild or moderate in severity.

No subject died during the course of the study. However, 1 subject (ABT-594 150 µg BID) died 58 days after completion of the Treatment Phase. The subject died due to suicide, which the investigator considered to be unrelated to study drug. In addition to the subject who died, 13 subjects (3 placebo, 4 ABT-594 150 µg, 2 ABT-594 225 µg, and 4 ABT-594 300 µg BID) experienced other serious adverse events. Eight of these subjects (2 placebo, 3 ABT-594 150 µg, 1 ABT-594 225 µg, and 2 ABT-594 300 µg BID) reported serious adverse events associated with the cardiovascular system during the study. Each subject had multiple risk factors for cardiovascular disease. One hundred subjects (6 placebo, 18 ABT-594 150 µg, 32 ABT-594 225 µg, and 44 ABT-594 300 µg BID) prematurely discontinued study drug due to 1 or more adverse events. The most frequently reported ($\geq 10\%$ of subjects in any ABT-594 treatment group) adverse events leading to discontinuation among ABT-594 subjects were nausea, dizziness, vomiting, abnormal dreams, and headache.

Results of other safety analyses, including individual subject changes, changes over time and individual clinically significant for laboratory evaluations, vital signs, ECGs, and physical examinations, were unremarkable for all treatment groups.

McCarthy Deposition Exhibit 48

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Part 4

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

14.0 Tables, Figures, and Graphs Referred to but not Included in the Text

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.0__1	Cross-Reference Listing of Summary Tables with Corresponding Source Listings	1
14.1	Demographic Data Summary Tables	
14.1__0	Abbreviations and Conventions	1
14.1__1.1	Number and Percentage of Subjects Contributed by Each Investigator (All Treated Subjects)	2
14.1__1.2	Number of Subjects Contributed by Each Investigator to All Treated Subjects, Intent-to-Treat Dataset, and Evaluable Dataset (All Treated Subjects)	2
14.1__2	Number and Percentage of Subjects Contributed by Each Protocol Version (All Treated Subjects)	1
14.1__3.1	Number and Percentage of Subjects Prematurely Discontinued (All Treated Subjects)	1
14.1__3.2	Listing of Subject Numbers by Reason for Premature Discontinuation From the Study (All Treated Subjects)	1
14.1__3.3	Subjects Who Prematurely Discontinued and Any Adverse Events for Which Study Drug was Prematurely Discontinued (All Treated Subjects)	41
14.1__3.4	Number of Subjects Prematurely Discontinued by days of Exposure to Study Drug (All Treated Subjects)	1
14.1__3.5	Number and Percentage of Subjects that Prematurely Terminated for Each Investigator (All Treated Subjects)	2
14.1__4.1	Summary of Demographic Characteristics (All Treated Subjects)	1
14.1__4.2	Summary of Demographic Characteristics (Evaluable Dataset)	1
14.1__4.3	Summary of Demographic Characteristics (Study Completers Dataset)	1
14.1__5.1	Summary of Medical History - Currently Symptomatic (All Treated Subjects)	4

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.1__5.2	Summary of Medical History - Not Currently Symptomatic (All Treated Subjects)	5
14.1__6	Summary of the Baseline Pain Assessments (All Treated Subjects)	1
14.1__7.1	Concurrent Medications Taken by Subjects During the Study (All Treated Subjects)	39
14.1__7.2	Listing of Subject Numbers by Therapeutic Clarifications Subjects Receiving Concurrent Medications During the Study (All Treated Subjects)	62
14.1__7.3	Ingredients and Therapeutic Classification of Concurrent Medications Received by Subjects During the Study (All Treated Subjects)	54
14.1__8	Summary of Treatment Exposure (All Treated Subjects)	1
14.2	Efficacy Data Summary Tables	
14.2__1.1	Summary of Reasons Subjects Excluded From the Intent-to-Treat Dataset (All Treated Subjects)	1
14.2__1.2	List of Subjects Excluded From the Intent-to-Treat Dataset (All Treated Subjects)	1
14.2__2.1.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__2.1.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__2.1.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Intent-to-Treat Dataset)	4
14.2__2.1.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Intent-to-Treat Dataset)	7

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__2.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__2.2	Homogeneity of Treatment Comparisons in the ANOVA for Subject Daily Diary (11-Point Likert Scale) for Baseline and Change From Baseline to Last Observation (Intent-to-Treat Dataset)	2
14.2__2.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) (Intent-to-Treat Dataset)	1
14.2__2.4.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Intent-to-Treat Dataset)	1
14.2__2.4.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Intent-to-Treat Dataset)	1
14.2__2.4.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Intent-to-Treat Dataset)	4
14.2__2.4.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Intent-to-Treat Dataset)	7
14.2__2.4.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment for Observed Cases (Intent-to-Treat Dataset)	1
14.2__3.1.1	Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__3.1.2	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Intent-to-Treat Dataset)	4

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__3.1.3	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__3.2	Homogeneity of Treatment Comparisons in the ANOVA for Site-Based 11-Point Likert Scale Pain Assessment for Baseline and Change From Baseline to Last Observation (Intent-to-Treat Dataset)	2
14.2__3.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment (Intent-to-Treat Dataset)	1
14.2__3.4	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment for Observed Cases (Intent-to-Treat Dataset)	4
14.2__4.1.1	Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__4.1.2	Analysis of Mean Change From Baseline to Final Visit for Each Item From the Neuropathic Pain Scale With Last Observation Carried Forward (Intent-to-Treat Dataset)	10
14.2__4.1.3	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score With Last Observation Carried Forward (Intent-to-Treat Dataset)	4
14.2__4.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Neuropathic Pain Scale Total Score With Last Observation Carried Forward (Intent-to-Treat Dataset)	1
14.2__4.2	Homogeneity of Treatment Comparisons in the ANOVA for the Neuropathic Pain Scale for Baseline and Change From Baseline to Last Observation (Intent-to-Treat Dataset)	2
14.2__4.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale - "Total Score" (Intent-to-Treat Dataset)	1

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__4.4	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score for Observed Cases (Intent-to-Treat Dataset)	4
14.2__5.1	Analysis of Global Impression of Change (Intent-to-Treat Dataset)	1
14.2__5.2	Analysis of Global Impression of Change -- Improved/Worsened (Intent-to-Treat Dataset)	1
14.2__5.3	Summary of Global Impression of Change Score (Intent-to-Treat Dataset)	1
14.2__5.4	Homogeneity of Treatment Comparisons in the ANOVA for Global Impression of Change (Intent-to-Treat Dataset)	2
14.2__6	Analysis of Mean Change From Baseline to Final Visit for SF-36 Health Status Survey (Acute) (Intent-to-Treat Dataset)	10
14.2__7.1	Analysis of Number of Subjects With Concomitant Analgesic Medication Use (Intent-to-Treat Dataset)	1
14.2__7.2	Analysis of Number of Subjects With Concomitant Analgesic Medication Use Within 24 Hours (Intent-to-Treat Dataset)	1
14.2__7.3	Analysis of Incidence of Concomitant Analgesic Medication Use Only for Subjects Using Concomitant Analgesic Medication (Intent-to-Treat Dataset)	2
14.2__8.1	Summary of Reasons Subjects Excluded From the Evaluable Dataset (All Treated Subjects)	1
14.2__8.2	List of Subjects Excluded From the Evaluable Dataset (All Treated Subjects)	4
14.2__9.1.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Evaluable Dataset)	1
14.2__9.1.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Evaluable Dataset)	1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__9.1.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Evaluable Dataset)	4
14.2__9.1.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Evaluable Dataset)	7
14.2__9.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment With Last Observation Carried Forward (Evaluable Dataset)	1
14.2__9.2	Homogeneity of Treatment Comparisons in the ANOVA for Subject Daily Diary (11-Point Likert Scale) for Baseline and Change From Baseline to Last Observation (Evaluable Dataset)	2
14.2__9.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) (Evaluable Dataset)	1
14.2__9.4.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Evaluable Dataset)	1
14.2__9.4.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Evaluable Dataset)	1
14.2__9.4.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Evaluable Dataset)	4
14.2__9.4.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Evaluable Dataset)	7
14.2__9.4.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment for Observed Cases (Evaluable Dataset)	1
14.2__10.1.1	Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Evaluable Dataset)	1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__10.1.2	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Evaluable Dataset)	4
14.2__10.1.3	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Evaluable Dataset)	1
14.2__10.2	Homogeneity of Treatment Comparisons in the ANOVA for Site-Based 11-Point Likert Scale Pain Assessment for Baseline and Change From Baseline to Last Observation (Evaluable Dataset)	2
14.2__10.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment (Evaluable Dataset)	1
14.2__10.4	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment for Observed Cases (Evaluable Dataset)	4
14.2__11.1.1	Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale With Last Observation Carried Forward (Evaluable Dataset)	1
14.2__11.1.2	Analysis of Mean Change From Baseline to Final Visit for Each Item From the Neuropathic Pain Scale With Last Observation Carried Forward (Evaluable Dataset)	10
14.2__11.1.3	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score With Last Observation Carried Forward (Evaluable Dataset)	4
14.2__11.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Neuropathic Pain Scale Total Score With Last Observation Carried Forward (Evaluable Dataset)	1
14.2__11.2	Homogeneity of Treatment Comparisons in the ANOVA for the Neuropathic Pain Scale for Baseline and Change From Baseline to Last Observation (Evaluable Dataset)	2

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__11.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale - "Total Score" (Evaluable Dataset)	1
14.2__11.4	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score for Observed Cases (Evaluable Dataset)	4
14.2__12.1	Analysis of Global Impression of Change (Evaluable Dataset)	1
14.2__12.2	Analysis of Global Impression of Change -- Better/Worse Only (Evaluable Dataset)	1
14.2__12.3	Summary of Global Impression of Change Score (Evaluable Dataset)	1
14.2__12.4	Homogeneity of Treatment Comparisons in the ANOVA for Global Impression of Change (Evaluable Dataset)	2
14.2__13	Analysis of Mean Change From Baseline to Final Visit for SF-36 Health Status Survey (Acute) (Evaluable Dataset)	10
14.2__14.1.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__14.1.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__14.1.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Study Completers Dataset)	4
14.2__14.1.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) With Last Observation Carried Forward (Study Completers Dataset)	7

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__14.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__14.2	Homogeneity of Treatment Comparisons in the ANOVA for Subject Daily Diary (11-Point Likert Scale) for Baseline and Change From Baseline to Last Observation (Study Completers Dataset)	2
14.2__14.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) (Study Completers Dataset)	1
14.2__14.4.1.1	Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Study Completers Dataset)	1
14.2__14.4.1.2	Results of Analysis of Mean Change From Baseline to Final Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Study Completers Dataset)	1
14.2__14.4.2	Analysis of Mean Change From Baseline to Each Visit From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Study Completers Dataset)	4
14.2__14.4.3	Analysis of Mean Change From Baseline to Each Week From Subject Daily Diary (11-Point Likert Scale) for Observed Cases (Study Completers Dataset)	7
14.2__14.4.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Subject Daily Diary (11-Point Likert Scale) Pain Assessment for Observed Cases (Study Completers Dataset)	1
14.2__15.1.1	Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__15.1.2	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Study Completers Dataset)	4

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__15.1.3	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Site-Based 11-Point Likert Pain Assessment With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__15.2	Homogeneity of Treatment Comparisons in the ANOVA for Site-Based 11-Point Likert Scale Pain Assessment for Baseline and Change From Baseline to Last Observation (Study Completers Dataset)	2
14.2__15.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for Site-Based 11-Point Likert Pain Assessment (Study Completers Dataset)	1
14.2__15.4	Analysis of Mean Change From Baseline to Each Visit for Site-Based 11-Point Likert Pain Assessment for Observed Cases (Study Completers Dataset)	4
14.2__16.1.1	Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__16.1.2	Analysis of Mean Change From Baseline to Final Visit for Each Item From the Neuropathic Pain Scale With Last Observation Carried Forward (Study Completers Dataset)	10
14.2__16.1.3	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score With Last Observation Carried Forward (Study Completers Dataset)	4
14.2__16.1.4	Analysis of Percentage of Subjects Responding to Treatment as Measured by the Neuropathic Pain Scale Total Score With Last Observation Carried Forward (Study Completers Dataset)	1
14.2__16.2	Homogeneity of Treatment Comparisons in the ANOVA for the Neuropathic Pain Scale for Baseline and Change From Baseline to Last Observation (Study Completers Dataset)	2
14.2__16.3	Dose-Response Analysis of Mean Change From Baseline to Final Visit for the Neuropathic Pain Scale - "Total Score" (Study Completers Dataset)	1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.2__16.4	Analysis of Mean Change From Baseline to Each Visit for the Neuropathic Pain Scale - Total Score for Observed Cases (Study Completers Dataset)	4
14.2__17.1	Analysis of Global Impression of Change (Study Completers Dataset)	1
14.2__17.2	Analysis of Global Impression of Change -- Improved/Worsened (Study Completers Dataset)	1
14.2__17.3	Summary of Global Impression of Change Score (Study Completers Dataset)	1
14.2__17.4	Homogeneity of Treatment Comparisons in the ANOVA for Global Impression of Change (Study Completers Dataset)	2
14.2__18	Analysis of Mean Change From Baseline to Final Visit for SF-36 Health Status Survey (Acute) (Study Completers Dataset)	10
14.3	Safety Data Summary Tables	
14.3.1	Displays of Adverse Events	
14.3.1__1.1	All Treatment-Emergent Adverse Events Grouped by Body System and COSTART Term (All Treated Subjects)	8
14.3.1__1.2.1	Severity of Treatment-Emergent Adverse Events Grouped by Body System and COSTART Term - Part 1 (All Treated Subjects)	8
14.3.1__1.2.2	Severity of Treatment-Emergent Adverse Events Grouped by Body System and COSTART Term - Part 2 (All Treated Subjects)	8
14.3.1__1.3.1	Relationship of Study Drug of Treatment-Emergent Adverse Events Grouped by Body System and COSTART Term - Part 1 (All Treated Subjects)	8
14.3.1__1.3.2	Relationship of Study Drug of Treatment-Emergent Adverse Events Grouped by Body System and COSTART Term - Part 2 (All Treated Subjects)	8
14.3.1__2.1	Incidence Across Time of Treatment-Emergent Adverse Events (All Treated Subjects)	17

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.3.1__2.2	Prevalence Across Time of Treatment-Emergent Adverse Events (All Treated Subjects)	13
14.3.1__3.1	Subject Numbers Associated With Treatment-Emergent Adverse Events Grouped by Body System, COSTART Term, Medical Term, and Description (All Treated Subjects)	23
14.3.1__3.2	Adverse Event Medical Terms and Descriptions Associated With Each COSTART Term (All Treated Subjects)	26
14.3.2	Listings of Deaths, Other Serious, and Significant Adverse Events	
14.3.2__1.1	Summary of Deaths (All Treated Subjects)	1
14.3.2__1.2	Summary of Serious Adverse Events (All Treated Subjects)	3
14.3.2__2	Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Terminated (All Treated Subjects)	18
14.3.2__3	Number and Percentage of Subjects With Treatment-Emergent Adverse Events for Which Study Drug was Prematurely Terminated Grouped by Body System and COSTART Term (All Treated Subjects)	3
14.3.3	Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events	
14.3.4	Laboratory Data	
14.3.4__1.0	Criteria for Potentially Clinically Significant Values for Laboratory, Vital Signs, and Electrocardiogram Variables	3
14.3.4__1.1	Mean Changes in Hematology Variables From Baseline to Minimum, Maximum, and Final Values (All Treated Subjects)	16
14.3.4__1.2	Mean Changes in Chemistry Variables From Baseline to Minimum, Maximum, and Final Values (All Treated Subjects)	20

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.3.4__1.3	Mean Changes in Urinalysis Variables From Baseline to Minimum, Maximum, and Final Values (All Treated Subjects)	2
14.3.4__2.1	Number and Percentage of Subjects With Shifts From Baseline to Final Value for Hematology Variables With Potentially Clinically Significant Criteria Used to Define Categories (All Treated Subjects)	15
14.3.4__2.2	Number and Percentage of Subjects With Shifts From Baseline to Final Value for Blood Chemistry Variables With Potentially Clinically Significant Criteria Used to Define Categories (All Treated Subjects)	19
14.3.4__2.3	Number and Percentage of Subjects With Shifts From Baseline to Final Value for Urinalysis Variables With Potentially Clinically Significant Criteria Used to Define Categories (All Treated Subjects)	7
14.3.4__3.1	Laboratory Determinations Meeting Criteria for Potentially Clinically Significant Values for Hematology Variables (All Treated Subjects)	7
14.3.4__3.2	Laboratory Determinations Meeting Criteria for Potentially Clinically Significant Values for Blood Chemistry Variables (All Treated Subjects)	31
14.3.4__3.3	Laboratory Determinations Meeting Criteria for Potentially Clinically Significant Values for Urinalysis Variables (All Treated Subjects)	7
14.3.4__4.1	Number and Percentage of Subjects With Potentially Clinically Significant Values for Hematology Variables (All Treated Subjects)	2
14.3.4__4.2	Number and Percentage of Subjects With Potentially Clinically Significant Values for Blood Chemistry Variables (All Treated Subjects)	2
14.3.4__4.3	Number and Percentage of Subjects With Potentially Clinically Significant Values for Urinalysis Variables (All Treated Subjects)	1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

<u>Table Number</u>	<u>Title</u>	<u>Number of Pages</u>
14.3.5	Displays of Vital Signs	
14.3.5__1	Mean Changes in Vital Signs and Weight From Baseline to Minimum, Maximum, and Final Values (All Treated Subjects)	5
14.3.5__2	Vital Signs and Weight Variables Meeting Criteria for Potentially Clinically Significant Values (All Treated Subjects)	1
14.3.5__3	Number and Percentage of Subjects With Potentially Clinically Significant Values for Vital Signs and Weight (All Treated Subjects)	1
14.3.6	Displays of Electrocardiograms	
14.3.6__1	Mean Changes in Electrocardiogram Variables From Baseline to Minimum, Maximum, and Final Values (All Treated Subjects)	5
14.3.6__2	Number and Percentage of Subjects With Shifts From Baseline to Final Value for Electrocardiogram Variables With Potentially Clinically Significant Criteria Used to Define Categories (All Treated Subjects)	4
14.3.6__3	Electrocardiogram Variables Meeting Criteria for Potentially Clinically Significant Values (All Treated Subjects)	4
14.3.6__4	Number and Percentage of Subjects With Potentially Clinically Significant Values for Electrocardiogram Variables (All Treated Subjects)	1

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Table 14.0_1
Cross-Reference Listing of Summary Tables with Corresponding Source Listings

Summary Table Number	Source Listing Number
14.1 1.1	16.2 4.1
14.1 1.2	16.2 3.1, 16.2 4.1
14.1 2	16.2 3.1, 16.2 3.3, 16.2 4.1
14.1 3.1, 14.1 3.2	16.2 1.1
14.1 3.3	16.2 1.1, 16.2 7.1.1
14.1 3.4, 14.1 3.5	16.2 1.1
14.1 4.1	16.2 4.1, 16.2 4.3
14.1 4.2, 14.1 4.3	16.2 3.1, 16.2 4.1, 16.2 4.3
14.1 5.1, 14.1 5.2	16.2 4.2
14.1 6	16.2 6.2.1, 16.2 6.2.2, 16.2 6.3.1
14.1 7.1, 14.1 7.2, 14.1 7.3	16.2 7.3
14.1 8	16.2 5.1.1, 16.2 5.1.2
14.2 1.1, 14.2 1.2	16.2 4.1, 16.2 6.2.1
14.2 2.1.1.1, 14.2 2.1.1.2	16.2 6.1, 16.2 6.2.1
14.2 2.1.2, 14.2 2.1.3, 14.2 2.1.4, 14.2 2.2, 14.2 2.3, 14.2 2.4.1.1, 14.2 2.4.1.2, 14.2 2.4.2, 14.2 2.4.3, 14.2 2.4.4	16.2 6.2.1
14.2 3.1.1, 14.2 3.1.2, 14.2 3.1.3, 14.2 3.2, 14.2 3.3, 14.2 3.4	16.2 6.2.2
14.2 4.1.1, 14.2 4.1.2, 14.2 4.1.3, 14.2 4.1.4, 14.2 4.2, 14.2 4.3, 14.2 4.4	16.2 6.3.1
14.2 5.1, 14.2 5.2, 14.2 5.3, 14.2 5.4	16.2 6.5
14.2 6	16.2 6.4.1, 16.2 6.4.2, 16.2 6.4.3
14.2 7.1, 14.2 7.2, 14.2 7.3	16.2 7.4
14.2 8.1, 14.2 8.2	16.2 3.1
14.2 9.1.1.1, 14.2 9.1.1.2, 14.2 9.1.2, 14.2 9.1.3, 14.2 9.1.4, 14.2 9.2, 14.2 9.3, 14.2 9.4.1.1, 14.2 9.4.1.2, 14.2 9.4.2, 14.2 9.4.3, 14.2 9.4.4	16.2 6.2.1
14.2 10.1.1, 14.2 10.1.2, 14.2 10.1.3, 14.2 10.2, 14.2 10.3, 14.2 10.4	16.2 6.2.2
14.2 11.1.1, 14.2 11.1.2, 14.2 11.1.3, 14.2 11.1.4, 14.2 11.2, 14.2 11.3, 14.2 11.4	16.2 6.3.1, 16.2 6.3.2
14.2 12.1, 14.2 12.2, 14.2 12.3,	16.2 6.5

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

14.2	12.4	
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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Table 14.0__1
Cross-Reference Listing of Summary Tables with Corresponding Source Listings (continued)

Summary Table Number	Source Listing Number
14.2__13	16.2__6.4.1, 16.2__6.4.2, 16.2__6.4.3
14.2__14.1.1.1, 14.2__14.1.1.2, 14.2__14.1.2, 14.2__14.1.3, 14.2__14.1.4, 14.2__14.2, 14.2__14.3, 14.2__14.4.1.1, 14.2__14.4.1.2, 14.2__14.4.2, 14.2__14.4.3, 14.2__14.4.4	16.2__6.2.1
14.2__15.1.1, 14.2__15.1.2, 14.2__15.1.3, 14.2__15.2, 14.2__15.3, 14.2__15.4	16.2__6.2.2
14.2__16.1.1, 14.2__16.1.2, 14.2__16.1.3, 14.2__16.1.4, 14.2__16.2, 14.2__16.3, 14.2__16.4	16.2__6.3.1, 16.2__6.3.2
14.2__17.1, 14.2__17.2, 14.2__17.3, 14.2__17.4	16.2__6.5
14.2__18	16.2__6.4.1, 16.2__6.4.2, 16.2__6.4.3
14.3.1__1.1, 14.3.1__1.2.1, 14.3.1__1.2.2, 14.3.1__1.3.1, 14.3.1__1.3.2, 14.3.1__2.1, 14.3.1__2.2, 14.3.1__3.1, 14.3.1__3.2	16.2__7.1.1
14.3.2__1.1, 14.3.2__1.2	16.2__7.1.1, 16.2__7.1.2
14.3.2__2, 14.3.2__3	16.2__7.1.1
14.3.4__1.1, 14.3.4__2.1, 14.3.4__3.1, 14.3.4__4.1	16.2__4.5.1, 16.2__4.5.2, 16.2__4.5.3, 16.2__4.5.4, 16.2__4.5.5, 16.2__8.2.1, 16.2__8.2.2, 16.2__8.2.3, 16.2__8.2.4, 16.2__8.2.5
14.3.4__1.2, 14.3.4__2.2, 14.3.4__3.2, 14.3.4__4.2	16.2__4.6.1, 16.2__4.6.2, 16.2__4.6.3, 16.2__4.6.4, 16.2__4.6.5, 16.2__4.6.6, 16.2__8.3.1, 16.2__8.3.2, 16.2__8.3.3, 16.2__8.3.4, 16.2__8.3.5, 16.2__8.3.6
14.3.4__1.3, 14.3.4__2.3, 14.3.4__3.3, 14.3.4__4.3	16.2__4.7.1, 16.2__4.7.2, 16.2__4.7.3, 16.2__4.7.4, 16.2__4.7.5, 16.2__8.4.1, 16.2__8.4.2, 16.2__8.4.3, 16.2__8.4.4, 16.2__8.4.5
14.3.5__1, 14.3.5__2, 14.3.5__3	16.2__9.1
14.3.6__1, 14.3.6__2, 14.3.6__3, 14.3.6__4	16.2__9.2

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Table 14.1__0

Abbreviations and Conventions

Explanation of entries labeled as TRT, RX DAY, SEGMENT NAME, SEGMENT INTERVAL, and SEGMENT DAY are described below.

The TRT entry refers to the treatment the subject received.

The RX DAY column shows the number of days since the start of drug dosing. If it is positive (negative), it indicates the number of days since (prior to) the start of the treatment period at the time of the observation. The first day of the treatment period is defined as RX DAY 1, while the last day prior to the start of the treatment period is defined as RX DAY -1.

The SEGMENT NAME column indicates whether an observation is from the prestudy or screening (PRE), double-blind (DB), or poststudy (POST) period. The SEGMENT INTERVAL shows the RX days in that segment. The SEGMENT DAY refers to the number of days from the start of that segment.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Deaths Among Placebo Subjects

No deaths were reported for placebo subjects during the study.

Deaths Among ABT-594 150 µg BID Subjects

INVESTIGATOR: Storey

SUBJECT NUMBER: 4100

A 56-year-old white female receiving ABT-594 150 µg BID died on Study Day 79 (76 days post-treatment) due to suicide (COSTART Term: suicide attempt). The subject was pronounced dead on arrival to the emergency room on Study Day 79 (76 days post-treatment) and autopsy confirmed death by hanging (suicidal). The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, depression and suicidal ideation over the past several years. The subject had discontinued study drug on Study Day 3 due to nightmares. The investigator considered the death by suicide to be not related to study drug and noted depression and history of suicidal ideation as the alternative etiologies.

Deaths Among ABT-594 225 µg BID Subjects

No deaths were reported for ABT-594 225 µg BID subjects during the study.

Deaths Among ABT-594 300 µg BID Subjects

No deaths were reported for ABT-594 300 µg BID subjects during the study.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Serious Adverse Events Among Placebo Subjects

INVESTIGATOR: DeBold

SUBJECT NUMBER: 4053

A 52-year-old white female receiving placebo was hospitalized on Study Day 52 (2 days post-treatment) due to ketoacidosis (COSTART Term: ketosis) and dehydration (COSTART Term: dehydration). The subject developed a headache, body aches, low-grade fever, nausea and vomiting and was diagnosed with ketoacidosis upon hospitalization. The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, pernicious anemia, Graves disease that resolved with I-131 treatment, gastroenteritis, and intermittent morning nausea with vomiting of bile (2-3 times per week on a regular basis). The subject reported having had 2 prior episodes (prior to study medication administration) of severe headache, body aches, low-grade fever, nausea and vomiting (described at the time as "flu") for which the subject went to the emergency room for re-hydration and insulin therapy. Admission blood glucose test indicated levels greater than 400 mg/dL. A computed tomography (CT) of the head, ECG and lumbar puncture were normal. Treatment medications included Toradol®, morphine sulfate, Benadryl®, Tylenol® and regular insulin. After symptoms improved, the subject was discharged on Study Day 53 (3 days post-treatment) within 24 hours of admission. The investigator considered the ketoacidosis as not related to study drug and noted viral gastroenteritis as an alternative etiology. The investigator considered the dehydration as not related to study drug and noted viral gastroenteritis as an alternative etiology.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4401

A 53-year-old white male receiving placebo was hospitalized on Study Day 42 (3 days post-treatment) for angina (COSTART Term: angina pectoris) and had prolongation of hospitalization due to atrial fibrillation (COSTART Term: fibrillation atrial) on Study Day 48 (9 days post-treatment). The subject reported chest tightness after walking on

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Study Day 34. Unspecified abnormalities on the ECG, stress test and echocardiogram indicated coronary artery disease and the subject was hospitalized on Study Day 42 (3 days post-treatment) for angioplasty. The subject's hospitalization was prolonged by the onset of atrial fibrillation on Study Day 48 (9 days post-treatment) and he was cardioverted that same day. The subject had a medical history of diabetes mellitus, diabetic retinopathy, obesity, mild hypertension and painful distal symmetric diabetic polyneuropathy. The subject also had a history of substernal chest pressure with an onset date of Study Day 11, which had not been reported prior to hospitalization. Treatment medications included Versed®, Diprivan®, Lasix®, heparin, protamine, sotalol hydrochloride, losartan, Plavix®, Cardizem CD® and Darvocet N-100®. The subject achieved successful cardioversion on Study Day 48 (9 days post-treatment). The subject received packed cells due to anemia secondary to blood loss during surgery. The subject was discharged on Study Day 49 (10 days post-treatment). The investigator considered the angina not related to study drug and noted coronary artery blockage as an alternative etiology.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4027

A 65-year-old white female receiving placebo was hospitalized on Study Day 9 (1 day post-treatment) due to stroke (COSTART Term: cerebrovascular accident). The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, prior stroke, hypertension, hyperlipidemia, hypothyroidism, clotting/bleeding problems, and menopause. A CT scan upon admission revealed "no acute changes". Two ECG's revealed "normal sinus rhythm, possible left atrial enlargement, anteriolateral T-wave abnormalities and possible ischemia." Laboratory tests were essentially normal except triglycerides were elevated and the HDL cholesterol was below normal. The subject's antiplatelet medication Plavix® was changed to Aggrenox®. The subject was discharged on Study Day 12 (4 days post-treatment). The investigator considered the stroke probably not related to study drug and noted high blood pressure and hypercholesterolemia as alternative etiologies.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Serious Adverse Events Among ABT-594 150 µg BID Subjects

INVESTIGATOR: Baunel

SUBJECT NUMBER: 4149

A 71-year-old white male receiving ABT-594 150 µg BID was hospitalized on Study Day 65 (15 days post-treatment) due to angina (COSTART Term: angina pectoris) and myocardial infarction (COSTART Term: infarct myocardial). The subject was referred to his primary care physician after 2 ECG's showed clinically significant changes (subject was asymptomatic). Upon presentation to the emergency room, the subject complained of chest pain from climbing the stairs and was admitted to the hospital. He was diagnosed as having a "silent" myocardial infarction sometime during the week prior to admittance to the hospital. The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, past alcoholism, hypertension, angina, coronary artery disease, myocardial infarction in 1994 with angioplasty, hypercholesterolemia, peripheral vascular disease and thrombocytopenia. Treatment included cardiac monitoring, intravenous nitroglycerin, oxygen and continuation of current medications. Cardiac enzymes were negative. The discharge ECG revealed "sinus bradycardia with occasional premature ventricular complexes; ST and marked T-wave abnormality (consider anterolateral ischemia); prolonged QT of 482 msec." The subject was discharged from the hospital on Study Day 66 (16 days post-treatment) with the angina and myocardial infarction resolved. The investigator considered the angina and myocardial infarction not related to study drug and noted arteriosclerosis caused by diabetes mellitus as an alternative etiology.

INVESTIGATOR: Fried

SUBJECT NUMBER: 4083

A 66-year-old white female receiving ABT-594 150 µg BID was hospitalized on Study Day 15 (1 day post-treatment) due to a syncopal episode (COSTART Term: syncope) and worsening of atrial fibrillation (COSTART Term: fibrillation atrial). The subject had a

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, hypertension, and a risk factor of a history of atrial fibrillation. No additional information is available about the event as the subject refused to release medical records. The investigator considered the syncopal episode as not related to study drug and noted rapid atrial fibrillation as an alternative etiology. The sponsor considered the syncopal episode possibly related to study drug. The investigator considered the worsening of atrial fibrillation as not related to study drug and noted a history of atrial fibrillation as an alternative etiology. The sponsor considered the worsening of atrial fibrillation as probably not related to study drug and noted history of atrial fibrillation as an alternative etiology.

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4070

A 48-year-old Hispanic female receiving ABT-594 150 µg BID was hospitalized on Study Day 10 due to pain in left arm, neck, shoulder and chest (COSTART Term: pain). The subject had a medical history of diabetes mellitus, hyperlipidemia, and painful distal symmetric diabetic polyneuropathy. The subject was placed in the cardiac telemetry unit with monitoring. The subject's arm, neck and chest pain was relieved after the administration of nitroglycerin. An ECG, stress test, chest x-ray, and laboratory studies were normal. The subject was discharged from the hospital on Study Day 14 (4 days post-treatment). Follow-up conducted on Study Day 15 (5 days post-treatment) revealed that the subject had no further chest or left arm pain. The investigator considered the pain not related to study drug and noted anxiety and/or stress as an alternative etiology.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4412

A 57-year-old white male receiving ABT-594 150 µg BID was hospitalized on Study Day 50 (1 day post-treatment) due to bilateral lower extremity ischemia (COSTART

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Term: peripheral vascular disorder). The subject complained of an increase in lower extremity pain starting approximately Study Day 36. On Study Day 50 (1 day post-treatment) the subject underwent a bilateral angioplasty to lower extremities. The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, past cigarette smoking, hypercholesterolemia, quadruple bypass and angioplasty to lower extremities in 1999. The subject was discharged from the hospital on Study Day 51 (2 days post-treatment) with improving symptoms. The investigator considered the bilateral lower extremity ischemia not related to study drug and noted atherosclerosis as an alternative etiology.

INVESTIGATOR: Storey

SUBJECT NUMBER: 4100 (see death narrative for this subject)

Serious Adverse Events Among ABT-594 225 µg BID Subjects

INVESTIGATOR: Kluge

SUBJECT NUMBER: 4133

A 66-year-old white male receiving ABT-594 225 µg BID was hospitalized on Study Day 6 due to chest pain with a final diagnosis of esophageal reflux disease (COSTART Term: esophageal reflux). The subject had a medical history of diabetes mellitus, dilated non-ischemic cardiomyopathy and congestive heart failure, hypertension, obesity, and painful distal symmetric diabetic polyneuropathy. Admission vital signs included a blood pressure of 189/86. Cardiac catheterization and coronary angiogram performed 7 months prior to study revealed "no evidence of coronary artery obstructive disease". A chest x-ray was normal, and an ECG revealed "normal sinus rhythm, bifascicular block, right bundle branch block (unchanged from previous ECGs)." A nitroglycerin drip was started which relieved the pain "somewhat". Laboratory results revealed no elevation of cardiac enzymes or troponin I level. Two days after Prevacid® was started, the chest pain had completely resolved, and the subject was discharged from the hospital on Study Day 9.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

(3 days post-treatment). The investigator considered the chest pain due to esophageal reflux not related to study drug and noted increased production of hydrochloric acid as an alternative etiology.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4451

A 60-year-old white female receiving ABT-594 225 µg BID was hospitalized on Study Day 18 due to shortness of breath (COSTART Term: shortness of breath) and angina (COSTART Term: angina pectoris). The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, myocardial infarction, coronary artery by-pass graft surgery, stroke, hypertension, hyperlipidemia, carotid endarterectomy, and a 40-pack per year history of smoking. Initial blood pressure was 200/90. After 2 nitroglycerin tablets and 15 minutes, blood pressure decreased to 170/85. An ECG performed on Study Day 18 revealed "normal sinus rhythm on a monitor rate of 70 with a normal axis, normal intervals, with ST depression in lateral leads and nonspecific ST and T wave changes consistent with her old ECG." A chest x-ray revealed no acute cardiopulmonary disease. Troponin and creatine phosphokinase (CPK) labs were normal. Treatment included nitroglycerin intravenously, aspirin, Lovenox[®], potassium and normal saline. A second ECG was performed on Study Day 19 and revealed "sinus bradycardia (54 bpm), left ventricular hypertrophy with QRS widening, ST and T wave abnormality, consider lateral ischemia". The subject was discharged from the hospital on Study Day 20 (2 days post-treatment) with no shortness of breath or anginal pain. The investigator considered the shortness of breath and anginal pain probably not related to study drug and noted anxiety and arthritis in the shoulder as an alternative etiology. The sponsor considered shortness of breath and anginal pain probably not related to study drug and noted history of significant cardiovascular disease as an alternative etiology.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Serious Adverse Events Among ABT-594 300 µg BID Subjects

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4002

A 70-year-old white male receiving ABT-594 150 µg BID (escalating to a final randomized dose of 300 µg BID) was hospitalized on Study Day 4 due to palpitations (COSTART Term: palpitation). The subject had a medical history of coronary artery bypass graft surgery, coronary angioplasty with stent placement, myocardial infarction, coronary artery disease, hyperlipidemia, diabetes mellitus, and painful distal symmetric diabetic polyneuropathy. An admission ECG showed "normal sinus rhythm, right bundle branch block, inferior infarct (age undetermined), and no acute ST changes." Admission labs revealed an elevated creatine kinase total value, but the creatine kinase MB and troponin values were normal. Subject continued his ongoing medical therapy consisting of insulin, aspirin (81mg), and Lipitor® and was observed for further symptoms. Creatine kinase MB and troponin values remained normal the following day. Repeat ECG on the day following admission showed "normal sinus rhythm, right bundle branch block, cannot rule out anterior infarct (age undetermined), inferior infarct (cited approximately 20 months prior to study drug), abnormal ECG, when compared with ECG of previous day the axis shifted left, and minimal criteria for anterior infarct were present" (discharge diagnosis did not include infarct, however). The subject was discharged from the hospital on Study Day 5 (1 day post-treatment). The investigator considered the palpitations probably related to study drug.

INVESTIGATOR: Holmlund

SUBJECT NUMBER: 4193

A 55-year-old white male receiving ABT-594 300 µg BID was hospitalized on Study Day 40 (32 days post-treatment) due to a hip fracture (COSTART Term: injury accidental). The subject suffered a fall while walking stairs. Evaluation revealed a hip fracture and the subject was hospitalized. The subject had a medical history of diabetes

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

mellitus, painful distal symmetric diabetic polyneuropathy, osteoarthritis, unsteadiness, and a risk factor of being unsteady secondary to his peripheral polyneuropathy. During hospitalization, the subject received "conservative treatment" of medication and buccal traction. Treatment medications included heparin sodium, Dilaudid®, Percocet®, Lortab®, insulin NPH, metformin, aspirin and hydromorphone. He was discharged 6 days later on Study Day 46 (38 days post-treatment). The investigator considered the fracture not related to study drug and noted accidental fall as an alternative etiology.

INVESTIGATOR: Holmlund

SUBJECT NUMBER: 4197

A 62-year-old white female receiving ABT-594 150 µg BID was hospitalized on Study Day 5 (1 day post-treatment) due to angina (COSTART Term: angina pectoris). The subject presented to the emergency room on Study Day 4 after experiencing near syncope and dizziness with chest and left arm pain. The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, hypertension, phlebitis, hypothyroidism, chronic diarrhea, and a risk factor of chest pain for the past week prior to hospitalization (not reported previously to the investigative site). Admission cardiac enzymes and a chest x-ray were normal, and an ECG showed "poor R-wave progression but no significant ECG abnormalities." An echocardiogram on Study Day 5 (1 day post-treatment) showed hypokinesis of the septum. A coronary angiogram with coronary stenting to the left anterior descending artery was performed on Study Day 8 (4 days post-treatment). Treatment medications included Lovenox®, nitroglycerin, Lipitor®, Plavix®, atenolol, Ecotrin®, ReoPro® and beta-blockers. The subject was discharged on Study Day 9 (5 days post-treatment). The investigator considered the angina to be probably not related to study drug and noted coronary artery disease as an alternative etiology.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4031

An 81-year-old white male receiving ABT-594 300 µg BID was hospitalized on Study Day 43 (7 days post-treatment) due to cellulitis of the right foot (COSTART Term: cellulitis). The subject had a medical history of diabetes mellitus, painful distal symmetric diabetic polyneuropathy, hyperlipidemia, coronary artery disease, coronary artery bypass graft, peripheral edema, bruising, and obesity. Admission laboratory studies showed an elevated WBC count, and subsequently, a blood culture showed β hemolytic strep. The subject was treated with Augmentin®, Unasyn®, and Ancef®. The subject was discharged from the hospital on Study Day 46 (10 days post-treatment) with the cellulitis improving. The investigator considered the cellulitis not related to study drug and noted secondary to possible strep infection as the alternative etiology.

Other Significant Adverse Events (Premature Discontinuations Due to Adverse Events)

Premature Discontinuations Due to Adverse Events Among Placebo Subjects

INVESTIGATOR: Gleeson

SUBJECT NUMBER: 4165

A 51-year-old Hispanic female randomized to placebo reported nausea, vomiting and diarrhea (COSTART Term: gastroenteritis) on Study Day 26 (1 day post-treatment). Study drug was discontinued on Study Day 25 and the event resolved on Study Day 35 (10 days post-treatment). The investigator considered the event of gastroenteritis probably not related to study drug and noted an alternative etiology of virus and taking study drug 25 days prior to onset.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kafka

SUBJECT NUMBER: 4419

A 61-year-old white female randomized to placebo reported worsening of nausea (COSTART Term: nausea) on Study Day 41 and bloating of abdomen (COSTART Term: flatulence) on Study 46. Study drug was discontinued on Study Day 46. The event of nausea resolved on Study Day 48 (2 days post-treatment); the event of bloating continued as of Study Day 65 (19 days post-treatment). The investigator considered the event of nausea as probably related to study drug. The investigator considered the event of bloating as probably not related to study drug and noted change in diet as an alternative etiology.

INVESTIGATOR: Kluge

SUBJECT NUMBER: 4136

A 71-year-old white male randomized to placebo reported a disconnected feeling and fell twice (COSTART Terms: depersonalization, accidental injury) on Study Day 25. Subject was incorrectly given the wrong module number on Study Day 1 and received 150 µg BID from Study Day 1 through Study Day 7. The correct module number was dispensed on Study Day 8 and the subject received placebo for the remainder of the study. Study drug was discontinued on Study Day 26. The event of falling lasted 3 minutes, and the event of feeling disconnected continued as of Study Day 30 (4 days post-treatment). The investigator considered the events of falling and feeling disconnected probably related to study drug.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4401 (see serious adverse event narrative for this subject)

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4021

A 65-year-old white male randomized to placebo reported an upper respiratory infection (COSTART Term: infection) on Study Day 8. Study drug was discontinued on Study Day 14, and the event resolved on Study Day 29 (15 days post-treatment). Treatment included Allegra-D®. The investigator considered the event of upper respiratory infection probably not related to study drug and noted infection and history of hayfever as alternative etiologies.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4027 (see serious adverse event narrative for this subject)

Premature Discontinuations Due to Adverse Events Among ABT-594 150 µg BID Subjects

INVESTIGATOR: DeBoh

SUBJECT NUMBER: 4060

A 57-year-old white male randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported lethargy, intermittent dizziness and worsened insomnia (COSTART Terms: somnolence, dizziness, and insomnia) on Study Day 1. Study drug was discontinued on Study Day 3 and the events resolved on the same day. The investigator considered the events of lethargy and dizziness probably related to study drug and the event of somnolence possible related to study drug noting an alternative etiology of increased pain and a history of insomnia.

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4003

A 78-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported blurred vision (COSTART Term: amblyopia) on Study Day 1. Study drug was discontinued on Study Day 2 and the event resolved on the same day. The subject had a history of macular degeneration. The investigator considered the event of amblyopia possibly related to study drug and noted an alternative etiology of macular degeneration.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Eisner

SUBJECT NUMBER: 4241

An 80-year-old white male randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea, vomiting, dizziness and intense sweating (COSTART Terms: nausea, vomiting, dizziness, sweating) on Study Day 1. Study drug was discontinued on the same day and the events of nausea, vomiting and sweating resolved on Study Day 2 (1 day post-treatment). The event of dizziness was treated with meclizine 12.5 mg QD and resolved on Study Day 4 (3 days post-treatment). The investigator considered the events of nausea, vomiting, dizziness, and sweating probably related to study drug.

INVESTIGATOR: Fried

SUBJECT NUMBER: 4083 (see serious adverse event narrative for this subject)

INVESTIGATOR: Haag

SUBJECT NUMBER: 4337

A 43-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 1 of the Titration Phase, reported dizziness (COSTART Term: dizziness) on Study Day 1. Study drug was discontinued on Study Day 6 and the event resolved the same day. The investigator considered the event of dizziness probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4066

A 54-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase), reported nausea (COSTART Term: nausea) on Study Day 2. Study drug was discontinued on Study Day 25, and the event resolved on Study Day 30 (5 days post-treatment). The investigator considered the event of nausea probably related to study drug.

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4070 (see serious adverse event narrative for this subject)

INVESTIGATOR: Kirby

SUBJECT NUMBER: 4182

A 56-year-old white female randomized to ABT-594 150 µg BID reported nausea (COSTART Term: nausea) on Study Day 7. Study drug was discontinued on Study Day 9 and the event resolved the same day. The investigator considered the event of nausea probably related to study drug.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4463

A 68-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported depressing dreams (COSTART Term: abnormal dreams) on Study Day 2. Study drug was discontinued on Study Day 6 and the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

event was reported as ongoing on Study Day 33 (27 days post-treatment). The investigator considered the event of abnormal dreams probably related to study drug.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4493

A 61-year-old white female randomized to ABT-594 150 µg BID reported stomach sickness/nausea (COSTART Term: dyspepsia) on Study Day 3 and headache (COSTART Term: headache) on Study Day 5. The subject was receiving 75 µg BID on Study Day 3 (Titration Phase) and had reached her randomization dose of 150 µg BID by Study Day 5. Study drug was discontinued on Study Day 14 and the events resolved on Study Day 15 (1 day post-treatment). The investigator considered the events of dyspepsia and headache probably related to study drug.

INVESTIGATOR: Simmons

SUBJECT NUMBER: 4276

A 56-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 3 (Titration Phase), reported nausea (COSTART Term: nausea) on Study Day 3. Study drug was discontinued on Study Day 19, and the event resolved on Study Day 31 (12 days post-treatment). The investigator considered the event probably related to study drug.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4402

A 67-year-old white female randomized to ABT-594 150 µg BID reported vomiting (COSTART Term: vomiting) on Study Day 11. Study drug was discontinued on Study

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Day 12 and the event resolved on Study Day 15 (3 days post-treatment). The investigator considered the event of vomiting probably related to study drug.

INVESTIGATOR: Sivakumar

SUBJECT NUMBER: 4041

A 51-year-old white female randomized to ABT-594 150 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase), reported nausea and vomiting (COSTART Terms: nausea, vomiting) on Study Day 1. Study drug was discontinued on Study Day 1, and the vomiting, lasting 5 minutes, resolved the same day. The event of nausea resolved on Study Day 4 (3 days post-treatment). The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Steel

SUBJECT NUMBER: 4209

A 68-year-old white male randomized to ABT-594 150 µg BID reported being lightheaded and dizzy (COSTART Term: dizziness) on Study Day 4. Study drug was discontinued on Study Day 23 and the event resolved on Study Day 42 (19 days post-treatment). The subject had a history of hypertension since 1996 and had a myocardial infarction and angioplasty in 1998. The investigator considered the event of dizziness possibly related to study drug and noted "cardiovascular" as an alternative etiology.

INVESTIGATOR: Steel

SUBJECT NUMBER: 4216

A 52-year-old black female randomized to ABT-594 150 µg BID reported nausea, bitter taste and vivid dreams (COSTART Terms: nausea, taste perversion, abnormal dreams) on Study Day 4 (Titration Phase). Study drug was discontinued on Study Day 5 and the

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

events resolved on Study Day 6 (1 day post-treatment). The investigator considered the events of *nausea, taste perversion and abnormal dreams probably related to study drug.*

INVESTIGATOR: Storey

SUBJECT NUMBER: 4100 (see death narrative for this subject)

INVESTIGATOR: Storey

SUBJECT NUMBER: 4109

A 46-year-old white female randomized to ABT-594 150 µg BID reported upset stomach and vomiting (COSTART Terms: dyspepsia, vomiting) on Study Day 29. Study drug was discontinued on Study Day 30, and the events resolved the same day. The investigator considered the events of upset stomach and vomiting probably related to study drug.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4020

A 73-year-old white female randomized to ABT-594 150 µg BID reported metallic taste, nausea and sore tongue (COSTART Terms: taste perversion, nausea, glossitis) on Study Day 21. Study drug was discontinued on Study Day 27, and the events resolved on Study Day 31 (4 days post-treatment). The investigator considered the events of metallic taste, nausea and sore tongue probably related to study drug.

Premature Discontinuations Due to Adverse Events Among ABT-594 225 µg BID Subjects

INVESTIGATOR: Bauml

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

SUBJECT NUMBER: 4147

An 85-year-old white male randomized to ABT-594 225 µg BID reported dizziness, decreased appetite, sweating and heartburn (COSTART Terms: dizziness, anorexia, sweating, dyspepsia) on Study Day 8. Study drug was discontinued on Study Day 11 and the events resolved the same day. The investigator considered the events of dizziness, decreased appetite, sweating and heartburn probably related to study drug.

INVESTIGATOR: Baumel

SUBJECT NUMBER: 4231

A 73-year-old white female randomized to ABT-594 225 µg BID reported visual hallucinations (COSTART Term: hallucinations) on Study Day 21. Study drug was discontinued on Study Day 21 and the event resolved the same day. The investigator considered the event of hallucination probably related to study drug.

INVESTIGATOR: Biton

SUBJECT NUMBER: 4257

A 60-year-old white female randomized to ABT-594 225 µg BID reported difficulty falling asleep and weakness (COSTART Terms: insomnia, asthenia) on Study Day 16. Study drug was discontinued on Study Day 37 and the events resolved on Study Day 40 (3 days post-treatment). The investigator considered the events of insomnia and asthenia probably related to study drug.

INVESTIGATOR: Bromberg

SUBJECT NUMBER: 4115

A 45-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase), reported nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 2. Study drug was discontinued on Study Day 6 (receiving randomized dose of 225 µg BID) and the events resolved on Study Day 7

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

(1 day post-treatment). The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Bromberg

SUBJECT NUMBER: 4118

A 48-year-old white male randomized to ABT-594 225 µg BID reported lightheadedness, headache and stomach pain (COSTART Terms: dizziness, headache, and abdominal pain) on Study Days 7, 8, and 11, respectively. Study drug was discontinued on Study Day 12 and the events resolved on Study Day 13 (1 day post-treatment). The investigator considered the events of dizziness, headache, and abdominal pain probably related to study drug.

INVESTIGATOR: Bromberg

SUBJECT NUMBER: 4125

A 65-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea, vomiting, dry heaves and dizziness (COSTART Terms: nausea, vomiting, dizziness) on Study Day 1. Study drug was discontinued on Study Day 2 and the events resolved on Study Day 3 (1 day post-treatment). The investigator considered the events of nausea, vomiting, and dizziness probably related to study drug.

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4001

A 72-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Days 1 and 2 (Titration Phase), reported insomnia (COSTART Term: insomnia) on Study Day 1 and reported dizziness and joint pain lower extremities (COSTART

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Terms: dizziness, arthralgia) on Study Day 2. Study drug was discontinued on Study Day 4, and all events resolved on Study Day 5 (1 day post-treatment). The investigator considered the events of insomnia, dizziness and joint pain probably related to study drug.

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4005

A 46-year-old white female randomized to ABT-594 225 µg BID reported nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 7 (Titration Phase). Study drug was discontinued on Study Day 8 and the events resolved on the same day. The subject was treated with Tigan® 100 mg as occasion requires (PRN). The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Forde

SUBJECT NUMBER: 4321

A 67-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported feeling anxious and having disturbing dreams (COSTART Terms: anxiety and abnormal dreams) on Study Day 2. Study drug was discontinued on Study Day 5 and the events resolved on the same day. The investigator considered the events of anxiety and abnormal dreams probably related to study drug.

INVESTIGATOR: Fried

SUBJECT NUMBER: 4089

An 80-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase), reported dizziness (COSTART Term: dizziness) on Study Day 2. Study drug was discontinued on Study Day 6, and the event resolved on

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Study Day 7 (1 day post-treatment). The investigator considered the event of dizziness probably related to study drug.

McCarthy Deposition Exhibit 48

P's Exhibit FZ

Part 5

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Gleeson

SUBJECT NUMBER: 4167

A 70-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported heartburn (COSTART Term: dyspepsia) on Study Day 2. Study drug was discontinued on Study Day 6 and the event resolved on Study Day 9 (3 days post-treatment). The investigator considered the event of dyspepsia probably related to study drug.

INVESTIGATOR: Haag

SUBJECT NUMBER: 4342

A 75-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea, vomiting and dizziness (COSTART Terms: nausea, vomiting, and dizziness) on Study Day 1. Study drug was discontinued on Study Day 1 and the event resolved on Study Day 2 (1 day post-treatment). The investigator considered the events of nausea, vomiting, and dizziness probably related to study drug.

INVESTIGATOR: Hewitt

SUBJECT NUMBER: 4311

A 52-year-old white male randomized to ABT-594 225 µg BID reported nausea and vomiting (COSTART Terms: nausea, vomiting) on Study Day 8. Study drug was discontinued on Study Day 8, and the events resolved on Study Day 9 (1 day post-treatment). The investigator considered the events of nausea and vomiting probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kafka

SUBJECT NUMBER: 4417

A 74-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Days 1 and 2 (Titration Phase), reported worsening of hypertension (COSTART Term: hypertension) on Study Day 1 and reported nausea (COSTART Term: nausea) on Study Day 2. Study drug was discontinued on Study Day 6 and the nausea resolved the same day. The event of hypertension resolved on Study Day 8 (2 days post-treatment). Treatment included Zestril® (started on Study Day 2). The investigator considered the events of hypertension and nausea possibly related to study drug and noted inadequate control of hypertension with current medication and new hypertension medication, respectively, as alternative etiologies.

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4075

A 74-year-old American Indian/Alaska native female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Days 1 and 3 (Titration Phase), reported mild nausea (COSTART Term: nausea) on Study Day 1 and severe nausea, shakiness, and funny feeling in legs making it difficult to walk, muscle aches (COSTART Terms: nausea, nervousness, gait abnormal, myalgia) on Study Day 3. Study drug was discontinued on Study Day 3, and the events of severe nausea, shakiness, gait abnormal and myalgia resolved after 2 hours on the same day. The event of mild nausea resolved on Study Day 18 (15 days post-treatment). Treatment included an emergency room evaluation and Phenergan®. The investigator considered the events of nausea, shakiness, gait abnormal and myalgia probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kirby

SUBJECT NUMBER: 4501

A 55-year-old white female randomized to ABT-594 225 µg BID reported unsteady gait (COSTART Term: abnormal gait) on Study Day 13. Study drug was discontinued on the same day and the event resolved on Study Day 14 (1 day post-treatment). The investigator considered the event of abnormal gait probably related to study drug.

INVESTIGATOR: Kluge

SUBJECT NUMBER: 4131

A 70-year-old white female randomized to ABT-594 225 µg BID reported blurred vision, dizziness, flatus and nausea (COSTART Terms: amblyopia, dizziness, flatulence, nausea) on Study Day 6 (Titration Phase) and reported aching, tired feeling and vomiting (COSTART Terms: pain, asthenia, vomiting) on Study Day 9. Study drug was discontinued on Study Day 9, and the events of dizziness, flatus, nausea and vomiting resolved the same day. The events of aching and tired feeling resolved on Study Day 32 (23 days post-treatment), and the event of blurred vision resolved on Study Day 41 (32 days post-treatment). The investigator considered the event of blurred vision possibly related to study drug and noted "diabetic" as an alternative etiology. The investigator considered the events of dizziness, nausea, tired feeling and vomiting possibly related to study drug and noted viral gastroenteritis as an alternative etiology. The investigator considered the events of aching and flatus probably not related to study drug and noted viral gastroenteritis as an alternative etiology.

INVESTIGATOR: Kluge

SUBJECT NUMBER: 4133 (see serious adverse event narrative for this subject)

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: McGill

SUBJECT NUMBER: 4387

A 66-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 3 (Titration Phase) reported dizziness, fatigue and malaise, nausea, nightmares, and sleeplessness (COSTART Terms: dizziness, asthenia, malaise, nausea, abnormal dreams, insomnia) on Study Day 3. Study drug was discontinued on Study Day 9, and all events resolved on Study Day 10 (1 day post-treatment). The investigator considered the events of dizziness, fatigue, malaise, nausea, nightmares, and sleeplessness probably related to study drug.

INVESTIGATOR: McGill

SUBJECT NUMBER: 4390

A 59-year-old white female randomized to ABT-594 225 µg BID reported palpitations (COSTART Term: palpitation) on Study Day 18. Study drug was discontinued on Study Day 17. The event resolved on Study Day 20 (3 days post-treatment). The investigator considered the event of palpitations possibly related to study drug and noted anxiety as an alternative etiology.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4451 (see serious adverse event narrative for this subject)

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4455

A 66-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 1, reported vomiting and stomach sickness (COSTART Terms: vomiting, dyspepsia) on Study Day 1 (Titration Phase). Study drug was discontinued on Study Day 1 and the events resolved on the same day. The investigator considered the events of vomiting and dyspepsia probably related to study drug.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4462

A 55-year-old white female randomized to ABT-594 225 µg BID reported stomach upset and nausea (COSTART Terms: dyspepsia, nausea) on Study Day 5, "fluttering" (COSTART Term: emotional lability) on Study Day 9, and diarrhea, confusion, moaning, crying, and shaking (COSTART Terms: diarrhea, confusion, emotional lability) on Study Day 10. Subject was receiving 150 µg BID on Study Day 5 (Titration Phase) and had reached her randomization dose of 225 µg BID by Study Day 9. Study drug was discontinued on Study Day 10 and the events resolved on the same day. The investigator considered the events of dyspepsia, emotional lability, diarrhea, and confusion probably related to study drug.

INVESTIGATOR: Simmons

SUBJECT NUMBER: 4275

A 69-year-old white female randomized to ABT-594 225 µg BID and receiving 150 µg BID on Study Day 5 and 225 µg BID from Study Day 6 (Titration Phase) on, reported nausea and vivid dreams (COSTART Terms: nausea, abnormal dreams) on Study Day 5, chills, headache and vomiting (COSTART Terms: chills, headache, vomiting) on Study

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Day 7, and diarrhea (COSTART Term: diarrhea) on Study Day 10. Study drug was discontinued on Study Day 10, and the event of vomiting resolved the same day. The events of chills, diarrhea, nausea, and vivid dreams resolved on Study Day 11 (1 day post-treatment). The event of headache resolved on Study Day 15 (5 days post-treatment). The investigator considered the events of chills, diarrhea, headache, nausea, vivid dreams, and vomiting probably related to study drug.

INVESTIGATOR: Simmons

SUBJECT NUMBER: 4277

A 56-year-old white female randomized to ABT-594 225 µg BID and receiving 225 µg BID from Study Day 6 (Titration Phase) on, reported nausea (COSTART Term: nausea) on Study Day 6 and vivid dreams (COSTART Term: abnormal dreams) on Study Day 9. Study drug was discontinued on Study Day 9, and the events resolved on Study Day 10 (1 day post-treatment). The investigator considered the events of nausea and vivid dreams probably related to study drug.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4404

A 60-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 3 (Titration Phase) reported insomnia (COSTART Term: insomnia) on Study Day 3. Study drug was discontinued on Study Day 17 and the event was reported as ongoing on Study Day 18 (1 day post-treatment). The investigator considered the event of insomnia probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Singer

SUBJECT NUMBER: 4408

A 70-year-old white female randomized to ABT-594 225 µg BID and receiving 150 µg BID on Study Day 5 (Titration Phase) reported vomiting (COSTART Term: vomiting) on Study Day 5. Study drug was discontinued on Study Day 10 and the event resolved on Study Day 11 (1 day post-treatment). The investigator considered the event of vomiting probably related to study drug.

INVESTIGATOR: Sivakumar

SUBJECT NUMBER: 4036

A 59-year-old white female randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported severe nausea (COSTART Term: nausea) on Study Day 2. Study drug was discontinued on Study Day 4. The event of severe nausea transitioned to mild nausea on Study Day 6 (2 days post-treatment), and the event of mild nausea resolved on Study Day 9 (5 days post-treatment). The investigator considered the event of severe nausea possibly related to study drug and noted possible flu, although afebrile, as an alternative etiology.

INVESTIGATOR: Sivakumar

SUBJECT NUMBER: 4040

A 57-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Days 1 and 3 and 150 µg BID on Study Day 5 (Titration Phase) reported irritability (COSTART Term: nervousness) on Study Day 1, diarrhea (COSTART Term: diarrhea) on Study Day 3, and burning eyes and vivid dreams (COSTART Terms: eye disorder, abnormal dreams) on Study Day 5. Study drug was discontinued on Study Day 7, and the events of diarrhea and vivid dreams resolved the same day. The event of

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

irritability resolved on Study Day 8 (1 day post-treatment), and the event of burning eyes resolved on Study Day 10 (3 days post-treatment). The investigator considered the events of diarrhea and vivid dreams possibly related to study drug and noted flu and "took antihistamine, rebound REM sleep", respectively, as alternative etiologies. The investigator considered the events of burning eyes and irritability probably not related to study drug and noted eye strain and not feeling well, respectively, as alternative etiologies.

INVESTIGATOR: Steel

SUBJECT NUMBER: 4212

A 56-year-old black female randomized to ABT-594 225 µg BID and receiving 75 µg on Study Day 1 reported tremors, increased blood pressure (160/100 mmHg), nausea, chills, increased pulse rate (108 bpm), chest discomfort, dizziness, visual hallucinations, nightmare, nervousness, loss of balance and headache (COSTART Terms: tremor, hypertension, nausea, chills, tachycardia, chest pain, dizziness, hallucinations, abnormal dreams, nervousness, ataxia, and headache) on Study Day 1. Study drug was discontinued on the same day and the events resolved on Study Day 2 (1 day post-treatment). The investigator considered the events of tremor, hypertension, nausea, chills, tachycardia, chest pain, dizziness, hallucinations, abnormal dreams, nervousness, ataxia, and headache probably related to study drug.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4022

A 60-year-old white male randomized to ABT-594 225 µg BID reported hair loss (COSTART Term: alopecia) on Study Day 9, nausea (COSTART Term: nausea) on Study Day 31, and vomiting (COSTART Term: vomiting) on Study Day 35. Study drug was discontinued on Study Day 36. The event of nausea resolved on Study Day 31 in 24 hours or less. The event of vomiting resolved on Study Day 37 (1 day post-treatment). The event of hair loss resolved on Study Day 138 (102 days post-treatment). The

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

investigator considered the events of nausea and vomiting probably related to study drug. The investigator considered the event of hair loss probably not related to study drug and noted extension of male pattern baldness as an alternative etiology.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4489

A 79-year-old white male randomized to ABT-594 225 µg BID and receiving 75 µg BID on Study Day 2 and 150 µg BID on Study Day 5 (Titration Phase) reported diarrhea and dizziness (COSTART Terms: diarrhea, dizziness) on Study Day 2 and reported feeling cold, hands numb (COSTART Term: chills, paresthesia) on Study Day 5. Study drug was discontinued on Study Day 6 after receiving 225 µg BID, and the event of feeling cold, hands numb resolved the same day. The events of diarrhea and dizziness resolved on Study Day 11 (5 days post-treatment). The investigator considered the events of diarrhea and dizziness probably related to study drug. The investigator considered the event of feeling cold, hands numb probably not related to study drug and noted secondary to diarrhea as an alternative etiology.

Premature Discontinuations Due to Adverse Events Among ABT-594 300 µg BID Subjects

INVESTIGATOR: Baumel

SUBJECT NUMBER: 4146

A 76-year-old white female randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 5 (Titration Phase) reported dizziness and headaches (COSTART Terms: dizziness, headache) on Study Day 5. Study drug was discontinued on Study Day 11. The event of headaches resolved on Study Day 16 (5 days post-treatment). The event of dizziness continued as of Study Day 21 (10 days post-treatment). The

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

investigator considered the events of dizziness and headaches probably related to study drug.

INVESTIGATOR: Baumel

SUBJECT NUMBER: 4232

A 71-year-old white male randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 3 (Titration Phase) reported nightmares and abdominal discomfort (COSTART Terms: abnormal dreams, abdominal pain) on Study Day 3. Study drug was discontinued on Study Day 4 and the events resolved on Study Day 5 (1 day post-treatment). The investigator considered the events of abnormal dreams and abdominal pain probably related to study drug.

INVESTIGATOR: Biton

SUBJECT NUMBER: 4260

A 61-year-old white male randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 4 (Titration Phase) reported feeling weak, dizzy, cold, clammy and "drunk" (COSTART Terms: asthenia, dizziness, chills, sweating, stupor) on Study Day 4. Study drug was discontinued on the same day and the subject was taken to the emergency room, where an ECG, MRI and laboratory tests were performed. The results of these tests were within normal limits and no other treatment was given. The events resolved on Study Day 5 (1 day post-treatment). The investigator considered the events of asthenia, dizziness, chills, sweating, and stupor probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Bromberg

SUBJECT NUMBER: 4113

A 69-year-old white female randomized to ABT-594 300 µg BID reported nausea (COSTART Term: nausea) on Study Day 5 and bizarre, unusual dreams (COSTART Term: abnormal dreams) on Study Day 11. Subject was receiving 150 µg BID on Study Day 5 (Titration Phase) and had reached the full randomization dose of 300 µg BID by Study Day 11. Study drug was discontinued on Study Day 18. The events resolved on Study Day 17. The investigator considered the events of nausea and abnormal dreams probably related to study drug.

INVESTIGATOR: Bromberg

SUBJECT NUMBER: 4117

A 50-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea and dizziness (COSTART Terms: nausea and dizziness) on Study Day 1. Study drug was discontinued on Study Day 8 and the events resolved on Study Day 9 (1 day post-treatment). The investigator considered the events of nausea and dizziness probably related to study drug.

INVESTIGATOR: DeBold

SUBJECT NUMBER: 4051

A 71-year-old white male randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 5 (Titration Phase) reported exacerbations of intermittent nausea, vomiting, lightheadedness and white halo visual disturbances (COSTART Terms: nausea, vomiting, dizziness, and abnormal vision) on Study Day 5. Study drug was discontinued on Study Day 11 and the events resolved on Study Day 12 (1 day post-treatment). The subject had a history of intermittent nausea, vomiting, lightheadedness and white halo visual

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

disturbances since 1997 and was symptomatic at the time of Screening. The subject was treated with Alka-Seltzer® and referred to his primary care physician. The investigator considered the events of nausea, vomiting, and dizziness probably related to study drug and the event of abnormal vision possibly related to study drug and noted an alternative etiology of history of intermittent white halo visual disturbances.

INVESTIGATOR: DeBold

SUBJECT NUMBER: 4055

A 75-year-old white male randomized to ABT-594 300 µg BID reported intermittent dull headaches and abdominal bloating (COSTART Terms: headache and abdomen enlarged) on Study Day 2 and intermittent nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 9. Subject was receiving 75 µg BID on Study Day 2 (Titration Phase) and had reached his randomization dose of 300 µg BID by Study Day 9. Study drug was discontinued on Study Day 15. The events of headache, nausea and vomiting resolved on Study Day 16 (1 day post-treatment) and the event of abdominal bloating resolved on Study Day 18 (3 days post-treatment). The investigator considered the events of headache, abdomen enlarged, nausea and vomiting probably related to study drug.

INVESTIGATOR: DeBold

SUBJECT NUMBER: 4057

A 72-year-old white male randomized to ABT-594 300 µg BID reported intermittent nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 12. Study drug was discontinued on Study Day 17 and the events resolved on the same day. The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4002 (see serious adverse event narrative for this subject)

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Drucker

SUBJECT NUMBER: 4006

A 72-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported generalized weakness, intense numbness throughout entire body and nightmare (COSTART Terms: asthenia, paresthesia, and abnormal dreams) on Study Day 2. Study drug was discontinued on Study Day 2 and the events resolved on the same day. The investigator considered the events of asthenia, paresthesia, and abnormal dreams probably related to study drug.

INVESTIGATOR: Eisner

SUBJECT NUMBER: 4243

A 68-year-old white male randomized to ABT-594 300 µg BID reported nausea and vomiting (COSTART Terms: nausea, vomiting) on Study Days 7 and 9, respectively. Subject was receiving 225 µg BID on Study Day 7 (Titration Phase) and had reached his randomized dose of 300 µg BID by Study Day 9. Study drug was discontinued on Study Day 11 and the events of nausea and vomiting resolved on Study Day 13 (2 days post-treatment). The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Eisner

SUBJECT NUMBER: 4246

A 77-year-old black female randomized to ABT-594 300 µg BID reported hyperglycemia (COSTART Term: hyperglycemia) on Study Day 14. Study drug was discontinued on Study Day 24. Subject was treated with Glucophage® 500 mg BID and Glucotrol XL® 10 mg BID and the event resolved on Study Day 35 (11 days post-treatment). The subject had a history of diabetes mellitus since 1983. The investigator considered the event of hyperglycemia probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Fried

SUBJECT NUMBER: 4087

A 74-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Days 1 and 2 (Titration Phase), reported diarrhea (COSTART Term: diarrhea) on Study Day 1 and reported fatigue, gastrointestinal upset and lightheadedness (COSTART Terms: asthenia, dyspepsia, dizziness) on Study Day 2. Study drug was discontinued on Study Day 4, and all events resolved on Study Day 6 (2 days post-treatment). The investigator considered the events of diarrhea, fatigue, GI upset and lightheadedness probably related to study drug.

INVESTIGATOR: Gibson

SUBJECT NUMBER: 4354

A 72-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported high blood pressure (180/115 mmHg), feeling flushed and energetic, warmth in legs, nausea, and nightmares (COSTART Terms: hypertension, vasodilation, nervousness, nausea, and abnormal dreams) on Study Day 2. Study drug was discontinued on Study Day 2 and the events resolved on the same day. The investigator considered the events of high blood pressure, feeling flushed and energetic, and warmth in legs as not related to study drug and noted underlying hypertension as an alternative etiology. The subject had a history of hypertension and has been treated with Avapro® 150 mg QD since 1985. The investigator considered the events of nausea and nightmares probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Gibson

SUBJECT NUMBER: 4359

A 31-year-old white male randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 3 (Titration Phase) reported nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 3. Study drug was discontinued on Study Day 27 and the events resolved on Study Day 28 (1 day post-treatment). Subject was treated with Phenergan®. The investigator considered the events of nausea and vomiting probably related to study drug.

INVESTIGATOR: Gibson

SUBJECT NUMBER: 4363

A 55-year-old white male randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 5 (Titration Phase) reported "chills - felt cold and clammy - then hot" (COSTART Term: chills) on Study Day 5. Study drug was discontinued on Study Day 14 and the event resolved on Study Day 15 (1 day post-treatment). The investigator considered the event of chills possibly related to study drug and noted an alternative etiology of infection.

INVESTIGATOR: Gibson

SUBJECT NUMBER: 4367

A 32-year-old white male randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 4 (Titration Phase) reported nausea and vomiting (COSTART Terms: nausea and vomiting) on Study Day 4. Study drug was discontinued on Study Day 12 and the event resolved on Study Day 13 (1 day post-treatment). The investigator considered the events of nausea and vomiting probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Gleeson

SUBJECT NUMBER: 4164

A 51-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported dizziness/light-headedness and disorientation (COSTART Terms: dizziness and confusion) on Study Day 2. Study drug was discontinued on Study Day 2 and the event resolved on the same day. The investigator considered the events of dizziness and confusion probably related to study drug.

INVESTIGATOR: Haag

SUBJECT NUMBER: 4340

A 72-year-old white male randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported sleep disturbances (COSTART Term: insomnia) on Study Day 1. Study drug was discontinued on Study Day 5 and the event resolved the same day. The investigator considered the event of insomnia probably related to study drug.

INVESTIGATOR: Haag

SUBJECT NUMBER: 4341

An 85-year-old white male randomized to ABT-594 300 µg BID reported mental status changes (COSTART Term: thinking abnormal) on Study Day 29. Study drug was discontinued on Study Day 36 and the event resolved on Study Day 40 (4 days post-treatment). The investigator considered the event of thinking abnormal probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Hewitt

SUBJECT NUMBER: 4309

A 76-year-old white male randomized to ABT-594 300 µg BID reported vomiting (COSTART Term: vomiting) on Study Day 24. Study drug was discontinued on Study Day 24 and the event resolved the same day. The investigator considered the event of vomiting probably related to study drug.

INVESTIGATOR: Hewitt

SUBJECT NUMBER: 4313

A 68-year-old black male randomized to ABT-594 300 µg BID reported flu symptoms (COSTART Term: flu syndrome) on Study Day 8. Study drug was discontinued on Study Day 8, and the event resolved on Study Day 15 (10 days post-treatment). The investigator considered the event of flu not related to study drug.

INVESTIGATOR: Holmlund

SUBJECT NUMBER: 4193 (see serious adverse event narrative for this subject)

INVESTIGATOR: Holmlund

SUBJECT NUMBER: 4197 (see serious adverse event narrative for this subject)

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kafka

SUBJECT NUMBER: 4420

A 76-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 3 and 300 µg BID on Study Day 8, reported insomnia (COSTART Term: insomnia) on Study Day 3 and reported aching jaw, heart palpitations and elevated blood pressure (COSTART Terms: pain, palpitation, hypertension) on Study Day 8. Study drug was discontinued on Study Day 8 and the jaw pain resolved the same day. The event of heart palpitations resolved on Study Day 9 (1 day post-treatment). The event of insomnia resolved on Study Day 11 (3 days post-treatment), and the event of elevated blood pressure resolved on Study Day 13 (5 days post-treatment). The investigator considered the event of jaw pain probably not related to study drug and noted heart palpitations as an alternative etiology. The investigator considered the events of heart palpitations, insomnia and elevated blood pressure possibly related to study drug and noted valve prosthesis, diabetic neuropathy and exacerbation of hypertension, respectively, as alternative etiologies.

INVESTIGATOR: Kafka

SUBJECT NUMBER: 4423

A 70-year-old white male randomized to ABT-594 300 µg BID and receiving 225 µg BID on Study Day 6 (Titration Phase) reported nausea (COSTART Term: nausea) on Study Day 6. Study drug was discontinued on Study Day 25 and the event resolved on Study Day 26 (1 day post-treatment). The investigator considered the event of nausea probably related to study drug.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4065

A 64-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea, headache, lightheadedness, chest tightness with no radiation, and redness around eye folds (COSTART Terms: nausea, headache, dizziness, chest pain, rash) on Study Day 1. Study drug was discontinued on Study Day 4, and all events except the rash resolved the same day. The event of rash resolved on Study Day 7 (3 days post-treatment). The investigator considered the events of nausea, headache, lightheadedness, chest tightness, and rash probably related to study drug.

INVESTIGATOR: Kipnes

SUBJECT NUMBER: 4072

A 69-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported nausea, belching, and abdominal discomfort (COSTART Terms: nausea, eructation, abdominal pain) on Study Day 1. Study drug was discontinued on Study Day 7, and the events resolved on Study Day 9 (2 days post-treatment). The investigator considered the events of nausea, belching, and abdominal discomfort possibly related to study drug and noted viral gastrointestinal syndrome as an alternative etiology.

INVESTIGATOR: Kirby

SUBJECT NUMBER: 4178

A 62-year-old white male randomized to ABT-594 300 µg BID reported a backache (COSTART Term: back pain) on Study Day 9. Study drug was discontinued on Study

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Day 10 and the event resolved on Study Day 12 (2 days post-treatment). The investigator considered the event of back pain probably related to study drug.

INVESTIGATOR: Kirby

SUBJECT NUMBER: 4184

A 57-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 3 and 150 µg BID on Study Day 4 reported dizziness and nausea (COSTART Terms: dizziness, nausea) on Study Days 3 and 4, respectively. Study drug was discontinued on Study Day 10 and the event resolved on Study Day 12 (2 days post-treatment). The investigator considered the events of dizziness and nausea probably related to study drug.

INVESTIGATOR: Kluge

SUBJECT NUMBER: 4135

A 60-year-old white female randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 4 (Titration Phase) reported aches in body, loose bowels, malaise, nausea, racing heart, vomiting and weird dreams (COSTART Terms: pain, diarrhea, malaise, nausea, tachycardia, vomiting, abnormal dreams) on Study Day 4. Study drug was discontinued on Study Day 4, and all events resolved on Study Day 6 (2 days post-treatment). The investigator considered the events of body aches, loose bowels, malaise, nausea, racing heart and vomiting not related to study drug and noted gastroenteritis as an alternative etiology. The investigator considered the event of weird dreams probably related to study drug.

INVESTIGATOR: Rowbotham

SUBJECT NUMBER: 4291

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

A 67-year-old white male randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 2 (Titration Phase) reported trouble breathing (COSTART Term: dyspnea) on Study Day 2. Study drug was discontinued on Study Day 19, and the event resolved on Study Day 23 (4 days post-treatment). The investigator considered the event of trouble breathing possibly related to study drug and noted intermittent sinusitis as an alternative etiology.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4450

A 58-year-old white female randomized to ABT-594 300 µg BID reported "nausea and epigastric pain" with a final diagnosis of GI upset (COSTART Term: dyspepsia) on Study Day 14. Study drug was discontinued on Study Day 30 and the event resolved on Study Day 33 (3 day post-treatment). The subject was treated with Phenergan[®] 25 mg PRN. The investigator considered the event of dyspepsia probably related to study drug.

INVESTIGATOR: Shaibani

SUBJECT NUMBER: 4456

A 57-year-old white male randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Days 1 and 3 and 225 µg BID on Study Day 7 reported headaches and lightheadedness (COSTART Terms: headache, dizziness) on Study Day 1, sleeplessness caused by stomach acids and depression (COSTART Terms: insomnia, depression) on Study Day 3, and rectal bleeding (COSTART Term: rectal hemorrhage) on Study Day 7. Study drug was discontinued on Study Day 7 and the events resolved on Study Day 8 (1 day post-treatment). The investigator considered the events of headache, dizziness and insomnia probably related to study drug and the events of rectal hemorrhage and depression possibly related to study drug noting alternative etiologies of hemorrhoids and pain, respectively.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

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ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

INVESTIGATOR: Simmons

SUBJECT NUMBER: 4273

A 58-year-old white male randomized to ABT-594 300 µg BID and receiving 150 µg BID on Study Day 5, 225 µg BID on Study Day 6, and 300 µg BID on Study Day 8 reported constriction-like feeling in chest, headache, stomach upset, and unusual dreams (COSTART Terms: chest pain, headache, dyspepsia, abnormal dreams) on Study Day 5, bad taste in mouth, body ache, cognitive dysfunction, and dry mouth (COSTART Terms: taste perversion, pain, thinking abnormal, dry mouth) on Study Day 6, nausea (COSTART Term: nausea) on Study Day 9, and bloating and decreased appetite (COSTART Terms: flatulence, anorexia) on Study Day 10. Study drug was discontinued on Study Day 11, and all events resolved on the same day. The investigator considered the events of chest pain, headache, stomach upset, unusual dreams, bad taste in mouth, body ache, cognitive dysfunction, dry mouth, nausea, bloating, and decreased appetite probably related to study drug.

INVESTIGATOR: Singer

SUBJECT NUMBER: 4403

A 57-year-old black female randomized to ABT-594 300 µg BID and receiving 225 µg BID on Study Day 6 (Titration Phase) reported insomnia (COSTART Term: insomnia) on Study Day 6. Study drug was discontinued on Study Day 33 and the event resolved on Study Day 35 (2 days post-treatment). The investigator considered the event of insomnia probably related to study drug.

INVESTIGATOR: Steel

SUBJECT NUMBER: 4210

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

A 73-year-old white male randomized to ABT-594 300 µg BID reported vomiting twice (COSTART Term: vomiting) on Study Day 9. Study drug was discontinued on Study Day 9, and the event resolved on Study Day 10 (1 day post-treatment). The investigator considered the event of vomiting probably related to study drug.

INVESTIGATOR: Steel

SUBJECT NUMBER: 4215

A 60-year-old white female randomized to ABT-594 300 µg BID reported nausea (COSTART Term: nausea) on Study Day 9. Study drug was discontinued on Study Day 9 and the event resolved on the same day. The investigator considered the event of nausea probably related to study drug.

INVESTIGATOR: Storey

SUBJECT NUMBER: 4098

A 70-year-old white female randomized to ABT-594 300 µg BID and receiving 150 µg on Study Day 4 (Titration Phase) reported nausea and weakness (COSTART Terms: nausea, asthenia) on Study Day 4. Study drug was discontinued on Study Day 8 and the events resolved the same day. The investigator considered the events of nausea and weakness probably related to study drug.

INVESTIGATOR: Storey

SUBJECT NUMBER: 4102

A 69-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Day 1 (Titration Phase) reported dizziness, nausea, pain and throbbing in head, unpleasant dream, vomiting, and weakness (COSTART Terms: nausea, headache, abnormal dreams, vomiting, asthenia) on Study Day 1. Study drug was discontinued on

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Study Day 2. The events of unpleasant dream and vomiting resolved on Study Day 1. The events of nausea and weakness resolved on Study Day 2. The events of dizziness and headache resolved on Study Day 3 (1 day post-treatment). The investigator considered the events of dizziness, headache, and weakness possibly related to study drug and noted diabetes as an alternative etiology. The investigator considered the events of nausea and vomiting possibly related to study drug and noted upset stomach as an alternative etiology. The investigator considered unpleasant dream possibly related to study drug and noted fatigue as an alternative etiology.

INVESTIGATOR: Storey

SUBJECT NUMBER: 4106

A 61-year-old white male randomized to ABT-594 300 µg BID and receiving 225 µg BID on Study Day 7 (Titration Phase) reported throbbing and pain in head, and unstable and lightheadedness (COSTART Terms: headache, dizziness) on Study Day 7. Study drug was discontinued on Study Day 11. The event of headache resolved on Study Day 10, and the event of dizziness resolved on Study Day 12 (1 day post-treatment). The investigator considered the events of headache and dizziness probably related to study drug.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4024

A 63-year-old white female randomized to ABT-594 300 µg BID and receiving 75 µg BID on Study Days 2 and 3 (Titration Phase) reported dizziness and nausea (COSTART Terms: dizziness, nausea) on Study Day 2, and reported gas, bilateral leg and foot cramps and sweating (COSTART Terms: flatulence, leg cramps, sweating) on Study Day 3. Study drug was discontinued on Study Day 7 and all events resolved on Study Day 10 (3 days post-treatment). The investigator considered the events of dizziness, nausea and gas probably related to study drug. The investigator considered the event of bilateral

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

leg/foot cramps possibly related to study drug and noted idiopathic muscle spasm as an alternative etiology. The investigator considered the event of sweating probably not related to study drug and noted GI upset as an alternative etiology.

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4031 (see serious adverse event narrative for this subject)

INVESTIGATOR: Weinstein

SUBJECT NUMBER: 4492

A 62-year-old white male randomized to ABT-594 300 µg BID reported a dislocated left shoulder (COSTART Term: accidental injury) on Study Day 20. Study drug was discontinued on Study Day 25. Treatment included Demerol® and Vicodin®. The event continued as of Study Day 73 (48 days post-treatment). The investigator considered the event of dislocated left shoulder not related to study drug and noted motor vehicle accident as the alternative etiology.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Table 14.3.4 _1.0
**Criteria for Potentially Clinically Significant Values for Laboratory,
 Vital Signs, and Electrocardiogram Variables**

Hematology	Very Low (VL)	Very High (VH)
Hemoglobin (g/dL)		
Female	≤ 9.5	≥ 16.5
Male	≤ 11.5	≥ 18.5
Hematocrit (%)		
Female	≤ 32	≥ 50
Male	≤ 37	≥ 55
Red Blood Cells (RBCs) ($\times 10^{12}/L$)		
Female	≤ 3.5	≥ 6.0
Male	≤ 3.8	≥ 7.0
White Blood Cells (WBCs) ($\times 10^9/L$)	≤ 2.8	≥ 16.0
Platelet Count ($\times 10^9/L$)	≤ 75	≥ 700
Eosinophils (%)		≥ 10
Basophils (%)		≥ 10
Lymphocytes (%)		≥ 75
Monocytes (%)		≥ 15
Neutrophils (%)	≤ 15	
Bands (%)		≥ 10
Mean Corpuscular Volume (MCV) (fL)	$\leq 0.8 \times LLN$	$\geq 1.2 \times ULN$
Mean Corpuscular Hemoglobin Concentration (MCHC) (g/dL)	$\leq 0.8 \times LLN$	$\geq 1.2 \times ULN$
Atypical Lymphocytes (%)		≥ 5
Prothrombin Time (PT) (sec)		$\geq 2 \times ULN$
Partial Thromboplastin Time (PTT) (sec)		$\geq 2 \times ULN$
LLN = Lower limit normal! ULN = Upper limit normal		

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Table 14.3.4_1.0
Criteria for Potentially Clinically Significant Values for Laboratory,
Vital Signs, and Electrocardiogram Variables (Continued)

Chemistry	Very Low (VL)	Very High (VH)
Albumin (g/dL)	≤2.5	
Alkaline Phosphatase (IU/L)		≥3 X ULN
Bicarbonate (mEq/L)	≤12	≥38
BUN (mg/dL)		≥30
Calcium (mg/dL)	≤8.2	≥12
Chloride (mEq/L)	≤90	≥118
Cholesterol (mg/dL)		≥600
Creatinine (mg/dL)		≥2.0
Direct Bilirubin (mg/dL)		≥2.0
Glucose (mg/dL)	≤45	≥175
LDH (IU/L)		≥3 X ULN
Inorganic Phosphorus (mg/dL)	≤1.7	≥5.5
Potassium (mEq/L)	≤3.0	≥6.0
SGOT/AST (IU/L)		≥3 X ULN
SGPT/ALT (IU/L)		≥3 X ULN
Sodium (mEq/L)	≤126	≥156
Total Bilirubin (mg/dL)		≥2.0
Total Protein (g/dL)	≤4.5	≥10
Triglycerides (mg/dL)		≥600
Uric Acid (mg/dL)		
Female		≥8.5
Male		≥10.5
ULN = Upper limit of normal		

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Table 14.3.4_1.0
Criteria for Potentially Clinically Significant Values for Laboratory,
Vital Signs, and Electrocardiogram Variables (Continued)

Urinalysis	Very Low (VL)	Very High (VH)
Specific Gravity	≤ 1.001	≥ 1.030
pH	≤ 4	≥ 9
Protein		$\geq 3+$ (≥ 10) ^a
Ketones		$\geq 3+$ ^a
RBC		
Female		$\geq 10/\text{hpf}$
Male		$\geq 8/\text{hpf}$
WBC		$\geq 10/\text{hpf}$ ($\geq 2+$)
Casts		≥ 9
Glucose		$\geq 3+$ ^a
Oral Body Temperature		
Temperature	Low: decreased $\geq 2^{\circ}\text{F}$ from baseline High: $\geq 101^{\circ}\text{F}$	
Supine or Sitting Vital Signs		
Systolic Blood Pressure	Low: ≤ 90 mm Hg and decreased ≥ 30 from baseline High: ≥ 180 mm Hg and increased ≥ 40 from baseline	
Diastolic Blood Pressure	Low: ≤ 50 mm Hg and decreased ≥ 20 from baseline High: ≥ 105 mm Hg and increased ≥ 30 from baseline	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	
Electrocardiogram		
PR Interval	High: ≥ 210 msec	
QRS Duration	Low: ≤ 50 msec High: ≥ 150 msec	
QT Interval	Low: ≤ 200 msec High: ≥ 500 msec	
QT _C Interval ^b	Low: ≤ 200 msec High: ≥ 500 msec	
Heart Rate	Low: ≤ 50 bpm and decreased ≥ 30 bpm from baseline High: ≥ 120 bpm and increased ≥ 30 bpm from baseline	
hpf = high power field		
^a $\geq 3+$ on a scale with 4+ being the maximum value.		
^b QT _C calculated as QT divided by the square root of RR interval.		

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

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ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

16.0 Appendices

List of Appendices

<u>Number</u>	<u>Title</u>	<u>Number of Pages</u>
16.1 Study Information		
16.1.1	Protocol and Protocol Amendments	
16.1.2	Sample Case Report Form (CRF)	
16.1.3	List of IEC/IRBS, Written Information for Subjects, and Representative Informed Consent	
16.1.4	List and Description of Investigators and Other Important Participants in the Study, Including Curricula Vitae	
16.1.5	Signature of Principal or Coordinating Investigator or Abbott Laboratories Responsible Medical Officer	
16.1.6	Listing of Subjects Receiving Test Drug(s)/ Investigational Product(s) from Specific Batches	5
16.1.7	Randomization Scheme and Codes	
16.1.8	Audit Certificates	
16.1.9	Documentation of Statistical Methods	12
16.1.10	Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures	
16.1.11	Publications Based on the Study	
16.1.12	Important Publications Referenced in the Report	
16.1.13	Efficacy Scales	

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

List of Appendices

<u>Number</u>	<u>Title</u>	<u>Number of Pages</u>
16.2	Subject Data Listings	
16.2__0	Abbreviations and Conventions	1
16.2__1.1	Subjects Who Prematurely Discontinued Study Drug Treatment	28
16.2__1.2	Other Medications and Supplements - Subjects Who Prematurely Discontinued	65
16.2__1.3	Subjects For Whom Blind Was Broken	1
16.2__2.1	Inclusion/Exclusion Criteria	47
16.2__2.2	Urine Drug Screen Results	44
16.2__2.3	Hepatitis Test Results	47
16.2__2.4	Pregnancy Test Results	20
16.2__3.1	Subjects Excluded From All Efficacy Evaluable Analyses	11
16.2__3.2	Data Excluded From Primary Efficacy Analyses	246
16.2__4.1	Subject Demographics	23
16.2__4.2	Subject Medical History	173
16.2__4.3	Tobacco and Alcohol Use	47
16.2__4.4	Physical Examination	108
16.2__4.5.1	Baseline Hematology Determinations - Part 1	62
16.2__4.5.2	Baseline Hematology Determinations- Part 2	62
16.2__4.5.3	Baseline Hematology Determinations - Part 3	62
16.2__4.5.4	Baseline Hematology Determinations - Part 4	63
16.2__4.5.5	Baseline Hematology Determinations - Comments and Values Outside the Reference Range	54
16.2__4.6.1	Baseline Chemistry Determinations - Part 1	62

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

List of Appendices (continued)

Number	Title	Number of Pages
16.2__4.6.2	Baseline Chemistry Determinations - Part 2	62
16.2__4.6.3	Baseline Chemistry Determinations - Part 3	62
16.2__4.6.4	Baseline Chemistry Determinations - Part 4	62
16.2__4.6.5	Baseline Chemistry Determinations - Part 5	62
16.2__4.6.6	Baseline Chemistry Determinations - Comments and Values Outside the Reference Range	83
16.2__4.7.1	Baseline Urinalysis Determinations - Part 1	62
16.2__4.7.2	Baseline Urinalysis Determinations - Part 2	62
16.2__4.7.3	Baseline Urinalysis Determinations - Part 3	62
16.2__4.7.4	Baseline Urinalysis Determinations - Part 4	63
16.2__4.7.5	Baseline Urinalysis Determinations - Comments and Values Outside the Reference Range	10
16.2__5.1.1	Study Drug Administration - Part 1	72
16.2__5.1.2	Study Drug Administration - Part 2	38
16.2__5.2	Excess Study Drug Administration	47
16.2__5.3.1	Plasma Assay Results - Part 1	53
16.2__5.3.2	Plasma Assay Results - Comments	4
16.2__6.1	Data Included In Primary Efficacy Analyses	113
16.2__6.2.1	Pain Assessment - Diary Based	347
16.2__6.2.2	Pain Assessment - Site Based	51
16.2__6.3.1	Neuropathic Pain Scale - Part 1	51
16.2__6.3.2	Neuropathic Pain Scale - Comments	1
16.2__6.4.1	Quality of Life - Part 1	43

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

List of Appendices (continued)

Number	Title	Number of Pages
16.2__6.4.2	Quality of Life - Part 2	45
16.2__6.4.3	Quality of Life - Comments	4
16.2__6.5	Global Impression of Change	37
16.2__7.1.1	Adverse Events	249
16.2__7.1.2	Serious Adverse Events	4
16.2__7.2	Subject Death	1
16.2__7.3	Other Medications and Supplements	42
16.2__7.4	Protocol Allowed Medications	64
16.2__8.1	Laboratory Reference Ranges	6
16.2__8.2.1	Hematology Determinations - Part 1	78
16.2__8.2.2	Hematology Determinations - Part 2	78
16.2__8.2.3	Hematology Determinations - Part 3	78
16.2__8.2.4	Hematology Determinations - Part 4	83
16.2__8.2.5	Hematology Determinations - Comments and Values Outside the Reference Range	99
16.2__8.3.1	Chemistry Determinations - Part 1	79
16.2__8.3.2	Chemistry Determinations - Part 2	78
16.2__8.3.3	Chemistry Determinations - Part 3	78
16.2__8.3.4	Chemistry Determinations - Part 4	78
16.2__8.3.5	Chemistry Determinations - Part 5	78
16.2__8.3.6	Chemistry Determinations - Comments and Values Outside the Reference Range	150
16.2__8.4.1	Urinalysis Determinations - Part 1	78

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

16.2__8.4.2 Urinalysis Determinations - Part 2

78

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

List of Appendices (continued)

Number	Title	Number of Pages
16.2__8.4.3	Urinalysis Determinations - Part 3	78
16.2__8.4.4	Urinalysis Determinations - Part 4	82
16.2__8.4.5	Urinalysis Determinations - Comments and Values Outside the Reference Range	18
16.2__9.1	Vital Signs	89
16.2__9.2	12-Lead Electrocardiogram Results	46

16.3 Case Report Forms (CRFs)

16.3.1	CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events	
16.3.2	Other CRFs Submitted	n/a

16.4 Individual Subject Data Listings

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.1
Protocol and Protocol Amendments

XXX Pages

Highly Confidential

ABBT238772

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.2
Sample Case Report Form (CRF)

XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.3

**List of IEC/IRBs, Written Information for Subjects, and Representative
Informed Consent**

XXX Pages

McCarthy Deposition Exhibit 48

P's Exhibit FZ

Part 6

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.4

**List and Description of Investigators and Other Important Participants
in the Study, Including Curricula Vitae**

XXX Pages

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ABBT238775

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.5

**Signatures of Principal or Coordinating Investigator(s) or Abbott
Laboratories Responsible Medical Officer**

XXX Pages

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ABBT238776

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.6

**Listing of Subjects Receiving Test Drug(s)/ Investigational Product(s)
from Specific Batches**

6 Pages

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ABBT238777

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 1

Appendix 16.1.6
Listing of Subjects Receiving Test Drug(s)/Investigational Product(s)
from Specific Batches

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
Backonja	4467	Placebo	No	No	Yes
	4466	ABT-594 150 µg BID	Yes	No	Yes
	4465	ABT-594 300 µg BID	Yes	No	Yes
Baumel	4148	Placebo	No	No	Yes
	4151	Placebo	No	No	Yes
	4227	Placebo	No	No	Yes
	4229	Placebo	No	No	Yes
	4145	ABT-594 150 µg BID	Yes	No	Yes
	4149	ABT-594 150 µg BID	Yes	Yes	Yes
	4226	ABT-594 150 µg BID	Yes	No	Yes
	4230	ABT-594 150 µg BID	Yes	Yes	Yes
	4147	ABT-594 225 µg BID	Yes	No	Yes
	4150	ABT-594 225 µg BID	Yes	No	Yes
	4228	ABT-594 225 µg BID	Yes	No	Yes
	4231	ABT-594 225 µg BID	Yes	Yes	Yes
	4146	ABT-594 300 µg BID	Yes	No	Yes
	4225	ABT-594 300 µg BID	Yes	No	Yes
	4232	ABT-594 300 µg BID	Yes	No	Yes
Biton	4258	Placebo	No	No	Yes
	4259	ABT-594 150 µg BID	Yes	Yes	Yes
	4261	ABT-594 150 µg BID	Yes	Yes	Yes
	4257	ABT-594 225 µg BID	Yes	No	Yes
	4262	ABT-594 225 µg BID	Yes	Yes	Yes
	4260	ABT-594 300 µg BID	Yes	No	Yes
	4263	ABT-594 300 µg BID	Yes	Yes	Yes
Bromberg	4116	Placebo	No	No	Yes
	4120	Placebo	No	No	Yes
	4122	Placebo	No	No	Yes
	4114	ABT-594 150 µg BID	Yes	No	Yes
	4119	ABT-594 150 µg BID	Yes	No	Yes
	4123	ABT-594 150 µg BID	Yes	No	Yes
	4115	ABT-594 225 µg BID	Yes	No	Yes
	4118	ABT-594 225 µg BID	Yes	No	Yes
	4124	ABT-594 225 µg BID	Yes	No	Yes
	4125	ABT-594 225 µg BID	Yes	No	Yes
	4113	ABT-594 300 µg BID	Yes	No	Yes
	4117	ABT-594 300 µg BID	Yes	No	Yes
DeBold	4121	ABT-594 300 µg BID	Yes	No	Yes
	4050	Placebo	No	No	Yes
	4053	Placebo	No	No	Yes
	4058	Placebo	No	No	Yes
	4052	ABT-594 150 µg BID	Yes	No	Yes

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ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 2

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
	4056	ABT-594 150 µg BID	Yes	Yes	Yes
DeBold (continued)	4060	ABT-594 150 µg BID	Yes	Yes	Yes
	4049	ABT-594 225 µg BID	Yes	No	Yes
	4054	ABT-594 225 µg BID	Yes	Yes	Yes
	4059	ABT-594 225 µg BID	Yes	Yes	Yes
	4051	ABT-594 300 µg BID	Yes	No	Yes
	4055	ABT-594 300 µg BID	Yes	No	Yes
	4057	ABT-594 300 µg BID	Yes	No	Yes
Drucker	4004	Placebo	No	No	Yes
	4003	ABT-594 150 µg BID	Yes	No	Yes
	4001	ABT-594 225 µg BID	Yes	No	Yes
	4005	ABT-594 225 µg BID	Yes	Yes	Yes
	4002	ABT-594 300 µg BID	Yes	No	Yes
	4006	ABT-594 300 µg BID	Yes	Yes	Yes
Eisner	4244	Placebo	No	No	Yes
	4241	ABT-594 150 µg BID	Yes	No	Yes
	4242	ABT-594 225 µg BID	Yes	No	Yes
	4245	ABT-594 225 µg BID	Yes	Yes	Yes
	4243	ABT-594 300 µg BID	Yes	No	Yes
	4246	ABT-594 300 µg BID	Yes	Yes	Yes
	4321	ABT-594 225 µg BID	Yes	No	Yes
Forde	4322	ABT-594 300 µg BID	Yes	No	Yes
	4084	Placebo	No	No	Yes
Fried	4085	Placebo	No	No	Yes
	4083	ABT-594 150 µg BID	Yes	No	Yes
	4086	ABT-594 150 µg BID	Yes	No	Yes
	4081	ABT-594 225 µg BID	Yes	No	Yes
	4088	ABT-594 225 µg BID	Yes	Yes	Yes
	4089	ABT-594 225 µg BID	Yes	No	Yes
	4082	ABT-594 300 µg BID	Yes	No	Yes
	4087	ABT-594 300 µg BID	Yes	No	Yes
	4356	Placebo	No	No	Yes
Gibson	4360	Placebo	No	No	Yes
	4364	Placebo	No	No	Yes
	4366	Placebo	No	No	Yes
	4487	Placebo	No	No	Yes
	4353	ABT-594 150 µg BID	Yes	Yes	Yes
	4357	ABT-594 150 µg BID	Yes	Yes	Yes
	4361	ABT-594 150 µg BID	Yes	Yes	Yes
	4368	ABT-594 150 µg BID	Yes	Yes	Yes
	4486	ABT-594 150 µg BID	Yes	Yes	Yes
	4355	ABT-594 225 µg BID	Yes	No	Yes
	4358	ABT-594 225 µg BID	Yes	Yes	Yes
	4362	ABT-594 225 µg BID	Yes	Yes	Yes
	4365	ABT-594 225 µg BID	Yes	Yes	Yes
	4354	ABT-594 300 µg BID	Yes	No	Yes
	4359	ABT-594 300 µg BID	Yes	Yes	Yes

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ABBT238779

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 3

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
Gibson	4363	ABT-594 300 µg BID	Yes	No	Yes
(continued)	4367	ABT-594 300 µg BID	Yes	No	Yes
Gleeson	4162	Placebo	No	No	Yes
	4165	Placebo	No	No	Yes
	4161	ABT-594 150 µg BID	Yes	No	Yes
	4166	ABT-594 150 µg BID	Yes	No	Yes
	4163	ABT-594 225 µg BID	Yes	No	Yes
	4167	ABT-594 225 µg BID	Yes	No	Yes
	4164	ABT-594 300 µg BID	Yes	No	Yes
Haag	4338	Placebo	No	No	Yes
	4337	ABT-594 150 µg BID	Yes	No	Yes
	4339	ABT-594 225 µg BID	Yes	Yes	Yes
	4342	ABT-594 225 µg BID	Yes	Yes	Yes
	4340	ABT-594 300 µg BID	Yes	No	Yes
	4341	ABT-594 300 µg BID	Yes	No	Yes
Hewitt	4308	Placebo	No	No	Yes
	4310	Placebo	No	No	Yes
	4306	ABT-594 150 µg BID	Yes	No	Yes
	4312	ABT-594 150 µg BID	Yes	Yes	Yes
	4311	ABT-594 225 µg BID	Yes	No	Yes
	4307	ABT-594 300 µg BID	Yes	No	Yes
	4309	ABT-594 300 µg BID	Yes	Yes	Yes
	4313	ABT-594 300 µg BID	Yes	No	Yes
Holmlund	4196	Placebo	No	No	Yes
	4195	ABT-594 150 µg BID	Yes	No	Yes
	4194	ABT-594 225 µg BID	Yes	No	Yes
	4193	ABT-594 300 µg BID	Yes	No	Yes
	4197	ABT-594 300 µg BID	Yes	No	Yes
Kafka	4419	Placebo	No	No	Yes
	4421	Placebo	No	No	Yes
	4418	ABT-594 150 µg BID	Yes	No	Yes
	4417	ABT-594 225 µg BID	Yes	No	Yes
	4422	ABT-594 225 µg BID	Yes	Yes	Yes
	4420	ABT-594 300 µg BID	Yes	No	Yes
	4423	ABT-594 300 µg BID	Yes	Yes	Yes
Kipnes	4067	Placebo	No	No	Yes
	4069	Placebo	No	No	Yes
	4076	Placebo	No	No	Yes
	4078	Placebo	No	No	Yes
	4066	ABT-594 150 µg BID	Yes	No	Yes
	4070	ABT-594 150 µg BID	Yes	No	Yes
	4073	ABT-594 150 µg BID	Yes	No	Yes
	4068	ABT-594 225 µg BID	Yes	No	Yes
	4071	ABT-594 225 µg BID	Yes	No	Yes
	4075	ABT-594 225 µg BID	Yes	No	Yes
	4077	ABT-594 225 µg BID	Yes	Yes	Yes
	4065	ABT-594 300 µg BID	Yes	No	Yes

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ABBT238780

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 4

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
Kipnes (continued)	4072	ABT-594 300 µg BID	Yes	No	Yes
	4074	ABT-594 300 µg BID	Yes	No	Yes
	4079	ABT-594 300 µg BID	Yes	Yes	Yes
Kirby	4177	Placebo	No	No	Yes
	4181	Placebo	No	No	Yes
	4502	Placebo	No	No	Yes
	4179	ABT-594 150 µg BID	Yes	No	Yes
	4182	ABT-594 150 µg BID	Yes	Yes	Yes
	4180	ABT-594 225 µg BID	Yes	Yes	Yes
	4183	ABT-594 225 µg BID	Yes	Yes	Yes
	4501	ABT-594 225 µg BID	Yes	Yes	Yes
	4178	ABT-594 300 µg BID	Yes	No	Yes
	4184	ABT-594 300 µg BID	Yes	No	Yes
	4132	Placebo	No	No	Yes
Kluge	4130	ABT-594 150 µg BID	Yes	No	Yes
	4134	ABT-594 150 µg BID	Yes	Yes	Yes
	4136	ABT-594 150 µg BID	Yes	No	Yes
	4131	ABT-594 225 µg BID	Yes	No	Yes
	4133	ABT-594 225 µg BID	Yes	No	Yes
	4129	ABT-594 300 µg BID	Yes	No	Yes
	4135	ABT-594 300 µg BID	Yes	No	Yes
	4137	ABT-594 300 µg BID	Yes	No	Yes
McGill	4386	Placebo	No	No	Yes
	4389	Placebo	No	No	Yes
	4388	ABT-594 150 µg BID	Yes	Yes	Yes
	4391	ABT-594 150 µg BID	Yes	Yes	Yes
	4387	ABT-594 225 µg BID	Yes	No	Yes
	4390	ABT-594 225 µg BID	Yes	No	Yes
	4385	ABT-594 300 µg BID	Yes	No	Yes
Rowbotham	4392	ABT-594 300 µg BID	Yes	Yes	Yes
	4292	Placebo	No	No	Yes
	4290	ABT-594 150 µg BID	Yes	No	Yes
	4289	ABT-594 225 µg BID	Yes	No	Yes
Shaibani	4291	ABT-594 300 µg BID	Yes	No	Yes
	4449	Placebo	No	No	Yes
	4454	Placebo	No	No	Yes
	4458	Placebo	No	No	Yes

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ABBT238781

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 5

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
Shaibani (continued)	4461	Placebo	No	No	Yes
	4452	ABT-594 150 µg BID	Yes	Yes	Yes
	4453	ABT-594 150 µg BID	Yes	Yes	Yes
	4457	ABT-594 150 µg BID	Yes	Yes	Yes
	4463	ABT-594 150 µg BID	Yes	Yes	Yes
	4493	ABT-594 150 µg BID	Yes	Yes	Yes
	4451	ABT-594 225 µg BID	Yes	Yes	Yes
	4455	ABT-594 225 µg BID	Yes	Yes	Yes
	4460	ABT-594 225 µg BID	Yes	Yes	Yes
	4462	ABT-594 225 µg BID	Yes	Yes	Yes
	4450	ABT-594 300 µg BID	Yes	Yes	Yes
	4456	ABT-594 300 µg BID	Yes	Yes	Yes
	4464	ABT-594 300 µg BID	Yes	Yes	Yes
	4494	ABT-594 300 µg BID	Yes	Yes	Yes
Simmons	4274	Placebo	No	No	Yes
	4276	ABT-594 150 µg BID	Yes	No	Yes
	4278	ABT-594 150 µg BID	Yes	Yes	Yes
	4275	ABT-594 225 µg BID	Yes	No	Yes
	4277	ABT-594 225 µg BID	Yes	No	Yes
	4273	ABT-594 300 µg BID	Yes	No	Yes
Singer	4401	Placebo	No	No	Yes
	4405	Placebo	No	No	Yes
	4409	Placebo	No	No	Yes
	4413	Placebo	No	No	Yes
	4402	ABT-594 150 µg BID	Yes	No	Yes
	4406	ABT-594 150 µg BID	Yes	Yes	Yes
	4412	ABT-594 150 µg BID	Yes	Yes	Yes
	4415	ABT-594 150 µg BID	Yes	Yes	Yes
	4404	ABT-594 225 µg BID	Yes	No	Yes
	4408	ABT-594 225 µg BID	Yes	Yes	Yes
	4410	ABT-594 225 µg BID	Yes	Yes	Yes
	4414	ABT-594 225 µg BID	Yes	Yes	Yes
	4403	ABT-594 300 µg BID	Yes	Yes	Yes
	4407	ABT-594 300 µg BID	Yes	Yes	Yes
	4411	ABT-594 300 µg BID	Yes	Yes	Yes
Sivakumar	4034	Placebo	No	No	Yes
	4039	Placebo	No	No	Yes
	4033	ABT-594 150 µg BID	Yes	No	Yes
	4038	ABT-594 150 µg BID	Yes	No	Yes
	4041	ABT-594 150 µg BID	Yes	No	Yes
	4036	ABT-594 225 µg BID	Yes	No	Yes
	4040	ABT-594 225 µg BID	Yes	No	Yes
	4035	ABT-594 300 µg BID	Yes	No	Yes
Steel	4037	ABT-594 300 µg BID	Yes	No	Yes
	4211	Placebo	No	No	Yes
	4214	Placebo	No	No	Yes

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ABBT238782

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 6

Investigator	Subject Number	Treatment Group	ABT-594 75 µg HGC Lot 58-293-AR	ABT-594 75 µg HGC Lot 61-312-AR	Placebo for ABT-594 Lot 55-243-AR-01
Steel (continued)	4209	ABT-594 150 µg BID	Yes	No	Yes
	4216	ABT-594 150 µg BID	Yes	No	Yes
	4212	ABT-594 225 µg BID	Yes	No	Yes
	4213	ABT-594 225 µg BID	Yes	Yes	Yes
	4210	ABT-594 300 µg BID	Yes	No	Yes
	4215	ABT-594 300 µg BID	Yes	No	Yes
Storey	4097	Placebo	No	No	Yes
	4101	Placebo	No	No	Yes
	4107	Placebo	No	No	Yes
	4100	ABT-594 150 µg BID	Yes	No	Yes
	4104	ABT-594 150 µg BID	Yes	Yes	Yes
	4105	ABT-594 150 µg BID	Yes	Yes	Yes
	4109	ABT-594 150 µg BID	Yes	Yes	Yes
	4099	ABT-594 225 µg BID	Yes	No	Yes
	4103	ABT-594 225 µg BID	Yes	Yes	Yes
	4108	ABT-594 225 µg BID	Yes	Yes	Yes
	4098	ABT-594 300 µg BID	Yes	No	Yes
	4102	ABT-594 300 µg BID	Yes	No	Yes
Suri	4435	Placebo	No	No	Yes
	4433	ABT-594 150 µg BID	Yes	No	Yes
	4434	ABT-594 300 µg BID	Yes	No	Yes
Vinik	4372	Placebo	No	No	Yes
	4374	Placebo	No	No	Yes
	4369	ABT-594 150 µg BID	Yes	Yes	Yes
	4370	ABT-594 150 µg BID	Yes	Yes	Yes
	4373	ABT-594 225 µg BID	Yes	Yes	Yes
	4371	ABT-594 300 µg BID	Yes	Yes	Yes
Weinstein	4017	Placebo	No	No	Yes
	4021	Placebo	No	No	Yes
	4027	Placebo	No	No	Yes
	4030	Placebo	No	No	Yes
	4491	Placebo	No	No	Yes
	4020	ABT-594 150 µg BID	Yes	No	Yes
	4023	ABT-594 150 µg BID	Yes	Yes	Yes
	4028	ABT-594 150 µg BID	Yes	Yes	Yes
	4029	ABT-594 150 µg BID	Yes	Yes	Yes
	4019	ABT-594 225 µg BID	Yes	No	Yes
	4022	ABT-594 225 µg BID	Yes	Yes	Yes
	4025	ABT-594 225 µg BID	Yes	Yes	Yes
	4032	ABT-594 225 µg BID	Yes	Yes	Yes
	4489	ABT-594 225 µg BID	Yes	Yes	Yes
	4018	ABT-594 300 µg BID	Yes	No	Yes
	4024	ABT-594 300 µg BID	Yes	Yes	Yes
	4026	ABT-594 300 µg BID	Yes	No	Yes
	4031	ABT-594 300 µg BID	Yes	Yes	Yes
	4492	ABT-594 300 µg BID	Yes	Yes	Yes

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ABBT238783

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.7

Randomization Scheme and Codes

XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.8
Audit Certificates

XXX Pages

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ABBT238785

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.9

Documentation of Statistical Methods

12 Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 1

Appendix 16.1.9 Documentation of Statistical Methods

All analyses were performed using SAS® version 6.12 (SAS Institute, Inc., SAS Campus Drive, Cary, NC 27513) on a Hewlett Packard workstation using the Unix operating system. All statistical tests were 2-tailed tests with a Type I error rate (alpha level) of 0.050. All p-values were rounded to 3 decimal places.

Analyses of variance (ANOVA) were performed with the SAS procedure GLM using Type III sums of squares for all tests of hypothesis. Model-based means were obtained from the LSMEANS statement for 2-way ANOVAs. Cochran-Mantel-Haenszel (CMH) and Fisher's exact tests were obtained from the FREQUENCY procedure. Univariate summary statistics (mean, standard deviation, median, minimum, maximum, first quartile and third quartile) were obtained from the UNIVARIATE procedure.

All subjects who received at least 1 dose of blinded study drug were included in the safety analyses. Three datasets, intent-to-treat (ITT), evaluable, and study completers, were defined for efficacy analyses. The ITT dataset included all subjects who received at least 1 dose of study drug and had at least 1 diary-based baseline and at least 1 post-dose pain assessment for the diary-based Pain Rating Scale (11-Point Likert Scale). The evaluable dataset included all subjects who received at least 7 days of study drug and had at least 1 baseline and at least 1 post Day 7 pain assessment for the diary-based Pain Rating Scale. The study completers dataset included those subjects who did not prematurely discontinue from the study for any reason.

16.1.9.1 Baseline Characteristics

Baseline comparability among the treatment groups for the reasons for premature discontinuation, demographic, medical history, and pain assessment variables (diary, site-based, and Neuropathic Pain Scale total score) was assessed by a 1-way ANOVA or CMH test, with treatment group as the main effect for the quantitative and ordered categorical variables, and by Fisher's Exact test extended for $r \times c$ tables for qualitative variables. Non-white races were combined for analysis of race. Additionally, users and ex-users were combined for analysis of nicotine use.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 2

16.1.9.2 Exposure

Duration of study drug exposure was summarized by treatment group. The difference among treatment groups was assessed using a 1-way ANOVA with treatment group as the main effect.

16.1.9.3 Efficacy Variables

Efficacy analyses were performed on the ITT and evaluable datasets.

The primary efficacy variable was the diary-based Pain Rating Scale (11-Point Likert Scale).

Secondary efficacy variables were the following:

1. Site-based Pain Rating Scale (11-Point Likert Scale),
2. Neuropathic Pain Scale,
3. Subject Global Impression of Change,
4. Clinician Global Impression of Change, and
5. SF-36™ Health Status Survey (Acute), including sub-domains [(i) Physical Functioning, (ii) Role Physical, (iii) Bodily Pain, (iv) General Health, (v) Vitality, (vi) Social Functioning, (vii) Role Emotional, (viii) Mental Health] PCS, and MCS.

16.1.9.4 Efficacy Analyses

For all efficacy variables (except the diary-based Pain Rating Scale), the baseline measurement was the last measurement obtained prior to receiving the first dose of blinded study drug on Day 1. Baseline for the diary-based Pain Rating Scale was the last 7 days of pain scores prior to Day 1 of the study. Change from baseline to each scheduled evaluation was calculated for all efficacy variables (except both Global Impression of Change scores).

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 3

Diary-Based Pain Rating Scale (11-Point Likert Scale)

The baseline pain score for diary data was defined as the average of the last 7 days of pain scores prior to Study Day 1 (with at least 4 non missing values). The subject diary was to be completed every day (at approximately 11 AM) during the Baseline Pain Assessment Phase (Study Days -7 to -1) and the Primer and Treatment Phases (Study Days 1 to 49). The Pain Rating Scale was an 11-Point Likert score, where 0=no pain and 10=worst pain possible. Diary data obtained on Day 1 (day of first dose was to be the PM dose only) and after each subject's last day of study drug dosing were excluded from all analyses. Additionally, subjects were required to have at least 4 non-missing post dose pain scores to be included in the analyses.

Primary Analyses

The primary analyses were the change from baseline of the average diary-based Pain Rating score from each subject's diary to the corresponding average of the diary scores during the last 7 days on study drug using last observation carried forward (LOCF). Dose-responses, with and without placebo, for the change to the last 7 days were also analyzed. For subjects who completed the study, the last 7 days on study drug were Study Days 43 to 49. For subjects who prematurely discontinued, the last 7 days on study drug were the last 7 days the subject was in the study. The LOCF analysis estimates missing data with the most recent non-missing data point. Use of the LOCF technique and the change from baseline to the average of the final 7 days on drug as the primary efficacy measure should have reduced bias caused by subjects who dropped out early due to lack of efficacy.

Treatment comparisons were made between placebo and each of the other treatment groups (i.e., ABT-594 150 µg, 225 µg, and 300 µg BID) using a 2-way ANOVA. The protocol-specified analysis for the 2-way ANOVA was a model with factors for treatment, study site, and the interaction between treatment and study site, if the interaction term was statistically significant. The interaction for the primary efficacy variable was not significant ($p>0.100$); therefore, the interaction term was not included in the model. Since the interaction was not significant for the primary efficacy variable, all efficacy analyses were done without the factor for interaction.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 4

Secondary Analyses

For all secondary analyses, except dose-response and homogeneity analyses, the change from baseline to the last 7 days on study drug for the diary-based Pain Rating Scale were also done using observed cases (OC). In these "observed cases" analyses missing data were not estimated as in the LOCF analyses.

Analyses were performed for the change from baseline to the last 7 days before each scheduled treatment visit and for the change from baseline to each of the consecutive 7-day intervals after the first dose of study drug. Treatment Visits I, II, III, and IV were to have been performed on Study Days 14, 21, 35, and 49, respectively. For the diary-based Pain Rating Scale, data recorded on the scheduled days were assigned to a visit the following way:

<u>Actual Day of Visit</u>	<u>Assigned Visit</u>
2 - 14	I
15 - 21	II
22 - 35	III
36 - 60	IV

Subjects who had at least 4 non-missing pain scores recorded in each interval were in the analysis for that interval. For subjects who did not have at least 4 non-missing scores for a specific interval, the average from the prior non-missing interval was used for that interval.

The proportion of subjects with specified percent changes from baseline to final was analyzed using a CMH test with study site as the stratification factor. For each of the baseline and final visits, homogeneity of treatment comparisons in the ANOVA model was analyzed using a 2-way ANOVA with factors for treatment, study site, and the interaction between treatment and study site.

Except where noted these analyses were performed using LOCF and OC techniques and used the same treatment comparisons as described for the primary diary analyses above.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 5

Site-Based Pain Rating Scale (11-Point Likert Scale)

Subjects were to assess pain intensity by completing the site-based Pain Rating Scale at the investigative site. These assessments were to be completed at the Baseline Visit and at Treatment Visits I, II, III, and IV (or upon premature discontinuation). The site-based Pain Rating Scale was an 11-Point Likert score, where 0=no pain and 10=worst pain possible. Data obtained after each subject's last day of study drug dosing were excluded from all analyses.

Primary Analyses

The primary analyses for the site-based Pain Rating Scale was the change from baseline to final visit using LOCF. Dose-responses, with and without placebo, for the change to final visit were also analyzed. For subjects who completed the study, the last site-based pain assessment was on Study Day 49. For subjects who prematurely discontinued, the last site-based pain assessment was the last day the subject was in the study. Using the change from baseline to the final visit as the primary efficacy measure should have reduced bias caused by subjects who dropped out early due to lack of efficacy.

Treatment comparisons were made between placebo and each of the other treatment groups (i.e., ABT-594 150 µg, 225 µg, and 300 µg BID) using a 2-way ANOVA, with factors for treatment and study site.

Secondary Analyses

Analyses of the site-based Pain Rating Scale were also performed for the change from baseline to each treatment visit (Treatment Visit I, II, III, and IV) using LOCF and OC techniques.

Treatment Visits I, II, III, and IV were to have been performed on days 14, 21, 35, and 49, respectively. Visits that were not performed on the scheduled day were assigned to a visit in the following way:

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 6

<u>Actual Day of Visit</u>	<u>Assigned Visit</u>
2 - 18	I
19 - 29	II
30 - 43	III
44 - 60	IV

If a visit was not completed, then the LOCF analysis used data from the previous completed visit as an estimate of the missing visit. Thus, in the LOCF analysis, every subject in the analysis had a value for each visit. This technique should have reduced bias caused by subjects who prematurely discontinued due to lack of efficacy. The "observed cases" analysis did not estimate any missing visits, so that a subject who did not have a certain visit was excluded from the "observed cases" analysis for that visit.

Additionally, the proportion of subjects with specified percent changes from baseline to final was analyzed using a CMH test with study site as the stratification factor. For each of the baseline and final visits, homogeneity of treatment comparisons in the ANOVA model was analyzed using a 2-way ANOVA with factors for treatment, study site, and the interaction between treatment and study site. These analyses were performed using only LOCF techniques.

Neuropathic Pain Scale

The baseline Neuropathic Pain score was defined as the last score on or before Day 1 of the study. The Neuropathic Pain Scale was to be completed during every site visit. The Neuropathic Pain Scale consists of 10 questions, with each question scored on a 0-10 scale with 0=none and 10=most. The Neuropathic Pain Scale total score consists of the sum of all 10 questions. Neuropathic Pain Scale data obtained after the last day of study drug dosing were excluded from all analyses.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 7

Primary Analyses

The primary analysis for the Neuropathic Pain Scale was the change from baseline to final visit using LOCF for the Neuropathic Pain Scale total score. For subjects who completed the study, the last Neuropathic Pain Scale was Day 49. For subjects who prematurely discontinued, the last Neuropathic Pain Scale was the last day the subject was in the study. Using the change from baseline to the final visit as the primary efficacy measure should have reduced bias caused by subjects who dropped out early due to lack of efficacy.

Treatment comparisons were made between placebo and each of the other treatment groups (i.e., ABT-594 150 µg, 225 µg, and 300 µg BID) using a 2-way ANOVA, with factors for treatment and study site.

Secondary Analyses

Analyses for the Neuropathic Pain Scale total score were also performed for the change to each treatment visit (Treatment Visit I, II, III, and IV) using LOCF. The change to each visit analyses were also performed using observed cases. Additionally, change from baseline to final visit for the individual item scores for each of the 10 Neuropathic Pain Scale questions was analyzed using LOCF.

Treatment Visits I, II, III, and IV were to have been performed on days 14, 21, 35, and 49, respectively. Visits that were not performed on the scheduled day were assigned to a visit in the following way:

<u>Actual Day of Visit</u>	<u>Assigned Visit</u>
2 - 18	I
19 - 29	II
30 - 43	III
44 - 60	IV

If a visit was not completed, the LOCF analysis used data from the previous completed visit as an estimate of the missing visit. Thus, in the LOCF analysis, every subject in the analysis had a value for each visit. This technique should have reduced bias caused by subjects who prematurely discontinued due to lack of efficacy. The "observed cases" analysis did not estimate any missing visits, so that a subject who did not have a certain visit was excluded from the "observed cases" analysis for that visit.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 8

Additionally, the proportion of subjects with specified percent changes from baseline to final was analyzed using a CMH test with study site as the stratification factor. For each of the baseline and final visits, homogeneity of treatment comparisons in the ANOVA model was analyzed using a 2-way ANOVA with factors for treatment, study site, and the interaction between treatment and study site. These analyses were performed using only LOCF techniques.

Missing Data Within a Visit

Since the Neuropathic Pain Scale total score consists of 10 questions at each visit, a method was used to estimate missing data when less than $\frac{1}{2}$ (5) of the questions were non-missing. This method is summarized below:

1. Calculate the ratio of the total score for the scale (non-missing questions) divided by the maximum possible total score of non-missing questions,
2. Multiply the maximum possible score of the missing question by the ratio obtained in step 1.

SF-36™ Health Status Survey (Acute)

Subjects were to complete the SF-36™ Health Status Survey at the Baseline Visit and at Treatment Visit IV (or upon premature discontinuation). Treatment group comparisons were made between placebo and each of the other treatment groups (i.e., ABT-594 150 µg, 225 µg, and 300 µg BID) for the 8 sub-domains, PCS, and MCS. The analyses were performed for the change from baseline to the final evaluation using a 2-way ANOVA with factors for treatment and study site. Data obtained after each subject's last day of study drug dosing were excluded from all analyses.

ABT-594 (ABBOTT-165594)
 Study No. M99-114
 R&D/01/171 - Clinical/Statistical

Appendix Page 9

Subject/Clinician Global Impression of Change

Both the Subject Global Impression of Change and the Clinician Global Impression of Change were to be performed when each subject either completed the study or prematurely discontinued. Impression of Change evaluation responses were based on a categorical scale, where 1= much improved, 2= moderately improved, 3= minimally improved, 4=no change, 5=minimally worse, 6=moderately worse, and 7=much worse. Impression of Change data obtained after the last day of study drug dosing were excluded from all analyses.

Primary Analysis

Treatment comparisons using univariate means were made between placebo and each of the other treatment groups (i.e., ABT-594 150 µg, 225 µg, and 300 µg BID) using a CMH test for equal row means with study site as the stratification factor.

Prior to analysis of the mean Impression of Change, scores were scaled to aid interpretation of results in the following way:

Response Choices	Precoded Item Value	Final Item Value
Much improved	1	3
Moderately improved	2	2
Minimally improved	3	1
No change	4	0
Minimally worse	5	-1
Moderately worse	6	-2
Much worse	7	-3

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 10

Secondary Analyses

The distributions for the Subject Global Impression of Change and the Clinician Global Impression of Change scores were analyzed using a CMH test for equal row means with study site as the stratification factor

Additionally, for each of the baseline and final visits, homogeneity of treatment comparisons in the ANOVA model was analyzed using a 2-way ANOVA with factors for treatment, study site, and the interaction between treatment and study site.

16.1.9.4 Concurrent Medications

Concurrent medication use was summarized by treatment group and by therapeutic classification and ingredient.

16.1.9.5 Safety Analyses

Adverse Events

A treatment-emergent adverse event was defined as any adverse event that began or worsened after the first dose of study drug. All treatment-emergent adverse events were mapped to the COSTART V dictionary. Subjects reporting more than 1 adverse event for a particular COSTART term were counted only once for that term using the most severe incident. Subjects reporting more than 1 type of event within a body system were counted only once for that body system.

Treatment-emergent adverse events were tabulated by COSTART term and body system for each treatment group and compared versus placebo using Fisher's exact test. A summary of the severity, relationship to study drug, incidence across time, and prevalence across time of all treatment-emergent adverse events, tabulated by COSTART term and body system, was presented for each treatment group.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 11

Laboratory Data

Baseline was defined as the last value on or before Study Day 1 for all laboratory analyses. Laboratory data obtained more than 2 days after the last dose of study drug were excluded from all analyses except for the listing of potentially clinically significant values.

Mean changes from baseline to minimum, maximum, and final values for each laboratory variable were analyzed using a 1-way ANOVA comparing placebo to each of the other treatments with treatment as the main effect. Additionally, the number and percentage of subjects with shifts from baseline to the final values using potentially clinically significant criteria and normal ranges to define categories (low, normal, high, and missing) were summarized.

Laboratory values outside the laboratory normal range were identified in the data listings. In addition, laboratory values which satisfied Abbott-specified criteria for potentially clinically significant values (Appendix 14.3.4__1.0) were summarized by treatment group and identified in the data listings. The proportion of subjects meeting potentially clinically significant criteria in each treatment group was also summarized. For a given laboratory variable, subjects in the denominator had to have a non-potentially clinically significant baseline and at least 1 post-baseline value, while subjects in the numerator had to have a non-potentially clinically significant baseline and at least 1 post-baseline value that met the potentially clinically significant criteria.

Vital Sign and Weight Data

Baseline was defined as the last value on or before Study Day 1 for all vital sign and weight analyses. Vital sign and weight data obtained more than 1 day after the last dose of study drug were excluded from all analyses except for the listing of potentially clinically significant values.

Mean changes from baseline to minimum, maximum, and final values for each vital sign and weight variable were analyzed using a 1-way ANOVA comparing placebo to each of the other treatments with treatment as the main effect.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix Page 12

Vital signs and weight values which satisfied Abbott-specified criteria for potentially clinically significant values (Appendix 14.3.4__1.0) were summarized by treatment group and identified in the data listings. The proportion of subjects meeting potentially clinically significant criteria in each treatment group was also summarized. For a given variable, subjects in the denominator had to have a baseline and at least 1 post-baseline value while subjects in the numerator had to have at least 1 value that met the potentially clinically significant criteria.

Electrocardiogram Data

Baseline was defined as the last value on or before Study Day 1 for all electrocardiogram (ECG) analyses. Electrocardiogram data performed more than 1 day after the last dose of study drug were excluded from all analyses except for the listing of potentially clinically significant values.

Mean changes from baseline to minimum, maximum, and final values for each ECG variable were analyzed using a 1-way ANOVA comparing placebo to each of the other treatments with treatment as the main effect. Additionally, the number and percentage of subjects with shifts from baseline to the final values using potentially clinically significant criteria to define categories (low, normal, high, and missing) were summarized.

Electrocardiogram values which satisfied Abbott-specified criteria for potentially clinically significant values (Appendix 14.3.4__1.0) were summarized by treatment group and identified in the data listings. The proportion of subjects meeting potentially clinically significant criteria in each treatment group was also summarized. For a given ECG variable, subjects in the denominator had to have a non-potentially clinically significant baseline and at least 1 post-baseline value while subjects in the numerator had to have a non-potentially clinically significant baseline and at least 1 post-baseline value that met the potentially clinically significant criteria.

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.10
Documentation of Inter-Laboratory Standardization Methods
and Quality Assurance Procedures

XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.11
Publications Based on the Study

xx Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.12
Important Publications Referenced in the Report
XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.1.13

Efficacy Scales

XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.2
Subject Data Listings

XXX Pages

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ABBT238803

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.3

Case Report Forms (CRFs)

XXX Pages

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.3.1
CRFs for Deaths, Other Serious Adverse Events and
Withdrawals for Adverse Events

XXX Pages

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ABBT238805

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.3.2

Other CRFs Submitted

XXX Pages

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ABBT238806

ABT-594 (ABBOTT-165594)
Study No. M99-114
R&D/01/171 - Clinical/Statistical

Appendix 16.4
Individual Subject Data Listings

Highly Confidential

ABBT238807

McCarthy Deposition Exhibit 52

P's Exhibit FX

Jul-01									
ABT-594: Neuronal Nicotinic Receptor Agent									
Franchise	Dev. Status	Brand Name	Generic Name	Patent Exp.	Indication(s)				
Neuroscience	Phase II	In progress	ebaniline tosylate	2016	Treatment of pain associated with diabetic polyneuropathy				
<p>ABT-594 is a neuronal nicotinic receptor with potential efficacy in nociceptive and neuropathic pain</p>									
U.S. Market	Unit	Value	CAGR	Unmet Need/Key Market Drivers			Key Competitor/Position to Market		
	TRX	10.5MM	6%	<p>US Significant unmet need in NP as many patients do not respond to currently available agents, many of which have unacceptable SEs. No branded marketed products currently indicated for NP (although Neurontin and/or pregabalin will likely be launched). Chronic persistent pain population is growing with aging population and also has high unmet need for non-opioid options with high efficacy</p>			<p>Neuropathic pain. Neurontin is taking strong lead in this market as increased MD awareness of efficacy coupled with ease of use becomes widespread, although it lacks an indication. Positive data and experience have made it first line in NP, although treatment patterns are diverse. Pregabalin is in development for NP also and may launch with indication before 594. Chronic pain likely some spillover prescribing in this market for 594. COX-2s and opioids dominate this market, but additional options (novel MOAs) with better efficacy than NSAIDs, without the AEs and addiction potential of opiates are needed for chronic pain.</p>		
Ex-US Market	TRX	23MM	3%	<p>Large unmet need. Agent with greater efficacy than currently available agents with adequate tolerability for chronic usage needed. Only one agent currently indicated for neuropathic pain (pregabalin - Lyrica).</p>			<p>Neuropathic pain. Gabapentin (Neurontin) on market with limited commercial success as US (initial 1999 sales 180 MM for use in all indications). Carbamazepine is gold standard treatment, but is not indicated for neuropathic pain, and has undesirable side effects. Pregabalin currently in Phase II. ABT-594 expected to be first to market NME for neuropathic pain. Chronic pain likely some spillover prescribing in this market for 594. Opiates reserved for only the most severe pain (e.g., cancer, post-op), thus large unmet need exists for non-scheduled, non-addictive agents for treatment of chronic pain.</p>		
	Sales	140MM	8%						
Development	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
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Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
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Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
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	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
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Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
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Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
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Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	TOTAL	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Cost to NDA	DDC	Est.	2000	2001	YTD	Proj.	Budget	Var.
	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Chronic	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
	Drug Safety	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0	\$0.0
Commercial	Other	\$0.0	\$0.0	\$0.0</					

July 2001

ABT-594

Monthly Highlights – Key Project Progress

- Maintenance activities only - Program is on hold pending Global Pharmaceutical Executive Committee meeting in August

Next Quarter's Key Progress Markers

Key Progress Marker

- Executive Committee review / Go - No Go target for program

Target Date
08/21

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact Cost Time Profile Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual In Process
Team has recommended implementation of the Mitsunobu chemistry change in step 4 of the synthetic process to eliminate the risk of mesylate impurity, which is potentially mutagenic.		<p>PARD Analytical has completed their analysis of the lab-scale batch made with the Mitsunobu chemistry change in step 4. No issues have been identified. Additional evaluation continues, looking at samples from the in-process chemistry stages to see if there are any additional targets to look for. Some degradation studies have been started, with final characterization and / or isolation to be completed.</p>	PARD Analytical	
		<p>The first production-scale lot of drug substance manufactured using the Mitsunobu chemistry change in step 4 has been completed. The specifications were issued 4/24 (document DTP-RD0838.) Release testing was completed in May, and the Certificate of Analysis will be released in June. Genotox testing has been proposed for this lot, but is currently pending feedback from PPD Toxicology. The lot was placed on stability in May, and the first pull is due in August.</p>	SPD / PARD Analytical / Toxicology	<p>Release testing complete: May</p> <p>QA release: TBD</p>

2 of 7

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July 2001

ABT-594

Key Project Issues and Risks

Risk or Issue	Potential or Known Impact Check all that apply and Describe Impact ___ Cost ___ Time ___ Profile ___ Regulatory	Strategy / Progress	Area / Responsibility	Resolution Date Planned / Actual
<p>During investigative work on implementation of the Mitsunobu chemistry route, a modification was made to the analytical method, which improved separation of some peaks. Using this method, an additional unknown impurity (designated as F¹) was detected in the lot of bulk drug used in M99-114 clinical capsules. Given the low exposure of M99-114 patients to F¹ and a lack of change in acute toxicity when this impurity was present in the drug substance, Toxicology does not view the presence of this impurity as a significant risk to these patients. However, further toxicology and pk testing of this impurity is necessary. Planned studies include Ames assay, in vitro micronucleus assay and bioavailability study</p>	<p>This issue has been reviewed with PARC, SPD, Toxicology, Regulatory and Venture Management. To date, the F¹ impurity has been detected at a level of 0.2% in the drug substance. Tentative identification including molecular structure has been made.</p> <ul style="list-style-type: none"> SPD has prepared the penultimate intermediate (1) to impurity F¹. 	<p>SPD</p>	<p>TBD</p>	
	<p>The first two attempts to reduce this compound to convert it to F¹ did not work. SPD is working with 30mg. We have gone back a couple steps and are preparing about 0.5g of intermediate 1, and will try some more reduction conditions. Plans are to have produced F¹ by mid-June.</p> <ul style="list-style-type: none"> PARC Analytical will be testing the F¹ material to confirm identity and match to impurity found in drug substance lot. When testing is successfully completed, F¹ material will be tested for genotoxicity by Toxicology and for bioavailability by Exploratory Kinetics. 	<p>PARC Analytical</p>	<p>TBD</p>	
	<p>___ Cost ___ Time ___ Profile ___ Regulatory</p>		<p>Toxicology / Exploratory Kinetics</p>	<p>TBD</p>

3 of 7

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July 2001**ABT-594****Key Activities**

Commercial		Formulation		Plan Date: 10/2000	
Activity	LBE	Actual	Activity	Plan	Actual
Qualitative conjoint analysis regarding commercial viability of various efficacy/AE profiles and associated market share tradeoffs	6/01	Completed in July/01	Phase I Formulation (PIB)* Clinical Supplies (PIB) for Molar Extraction	7/1997	7/1997
Qualitative market research regarding attractiveness of transdermal patch for severe pain or neuropathic pain patients	6/01	Suspended due to Pending/Terminated status	Phase II Formulation (SEC) for IND Clinical Supplies (SEC) Shipped (Osteoarthritis, Surgery, Neuropathy)	7/1998 7/1998 10/1998	7/1998 7/1998 10/1998
NMR communication strategy	12/01	Suspended due to Pending/Terminated status	Phase IIb / Formulation (HGC) for Bio Study	3/1999	3/1999
ABT 594 publication plan	12/01	Suspended due to Pending/Terminated status	Phase III Clinical Supplies Manufactured NDA Lots (3) Completed Completion of 1 Year Stability for NDA Formulation Peer Review	9/2001 5/2002 7/2003 TBD	TBD TBD TBD TBD
Brand name registration submission (generic name approved 11/00 - ebacaine tosylate)	12/01	Suspended due to Pending/Terminated status			

* Performed by IDC

4 of 7

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July 2001

ABT-594

Drug Substance				Plan Date: 6/1999		Toxicology			Plan Date: 1999	
Activity	KG	Plan	Actual	Actual / Projected Cost/kg*		Toxicology Activity	Planned Start	Actual Start Date	Report Completed	
D-45L	0.3 KG	3/1997	3/1997	\$ 200,000		Gene Toxicology	2/1997	9/1996	8/1997	
CAPD	5.6 KG	3/1997	3/1997	\$ 175,000		Acute Studies	3/1997	4/1997	8/1997	
SICOR	14.9 KG	2/1998	2/1998	\$ 40,000		1 Month Rat/Monkey	2/1997	2/1997	11/1997	
SICOR/CAPD	2.5 KG	8/1998	8/1998	\$ 40,000		3 Month Rat/Monkey	7/1997	8/1997	8/1998	
ChemSyn Pilot Lot	1.0 KG	5/1999	5/1999	\$ 29,700		3 Month Mouse MTD	10/1997	6/1997	10/1998	
ChemSyn Mfg Lot	10.0 KG	10/1999	Not manufactured	\$ 29,700		SEG I and SEG II	10/1997	7/1997	7/1998	
ChemSyn NDA Lot #1 (Mesylate)	4.85 KG	10/1999	2/2001 **	\$ 29,700		SEG III Rat (post natal development)		1/1999	Ongoing	
ChemSyn NDA Lot #2 (Mesylate)	4.80 KG	10/1999	2/2001 **	\$ 29,700		6 Month Rat	1/1998	3/1998	7/1999	
ChemSyn NDA Lot #3 (Mesylate)	5.45 KG	10/1999	2/2001 **	\$ 29,700		1 Year Monkey	6/1998	6/1998	3/2000	
ChemSyn Misunobu Lot#1	5.0 KG	04/2001	On Test.			Carcinogenicity (2 yr.) Rat	12/1998	9/1998	Ongoing *	
ChemSyn Misunobu Lot#2	5.0 KG		04/2001			Carcinogenicity (2 yr.) Mouse	12/1998	11/1998	Ongoing *	
ChemSyn Misunobu Lot#3	5.0 KG					* In-life phase complete, and analysis / assessment in process				

* Target cost of drug substance at launch is \$20,000/kg (Tosylate Salt)

** Bulk manufactured 1/2000, but delivery delayed due to Mesylate testing & QA release

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5 of 7

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July 2001**ABT-594****All Clinical Studies:**

Protocol Number	Phase	Study Name	Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients		Start 1 st Pt. Dosed	End (Last CRF In)	Patients	
								Target	Current			Target	Current
M99-114	II	Safety & Efficacy vs placebo in Panitumumab Diabetic Neuropathy				04/00	04/01	320	269 Final				

6 of 7

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July 2001**ABT-594****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M99-114 – A Randomized, Double-Blind, Placebo-Controlled Comparison of the Safety and Efficacy of ABT-594 to Placebo in Subjects with Painful

Diabetic Polyneuropathy

Objective: The objective of this study is to compare the safety and analgesic efficacy of 150 µg, 225 µg, and 300 µg twice daily (BID) of ABT-594 to placebo in subjects who have painful distal symmetric diabetic polyneuropathy.

ABT-594 Doses: 150 µg, 225 µg, and 300 µg twice daily (BID)

Comparator Doses: Placebo

Target Enrollment: 320

Status: Enrollment Complete – 269 patients randomized

Major Findings: TBD

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7 of 7

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McCarthy Deposition Exhibit 54

D's Exhibit 661

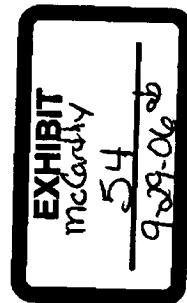
Part 1

ABT-594 GPEC Review

August 21, 2001

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ABBT311519



ABT-594 August 2001 GPEC Review

- Development Update Bruce McCarthy
- DSG Analysis Steve Kuemmerle
Liz Kowaluk
- NNR Follow-ons Michael Meyer

August 15, 2001

2

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ABBT311520

ABT-594 August 2001 GPEC Review Topics

- ABT-594 efficacy in neuropathic pain is significant
 - ABT-594 has a narrow therapeutic window and efficacious doses are poorly tolerated as dosed currently
 - Modifications to drug administration have the potential to improve tolerability
- Decision analysis suggests that the expected value for these modifications (to improve tolerability) is small, although positive
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

August 15, 2001

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ABBT311521

ABT-594's Potential for Pain Relief

- Efficacy across preclinical models of pain
 - Efficacy of morphine without morphine-like adverse events
 - Efficacy in neuropathic pain
- Commercial and clinical development plan targeted acute and chronic nociceptive pain and neuropathic pain, based upon preclinical promise
- Tolerability/onset of action issues made neuropathic pain relatively more attractive
 - Dosages that provide meaningful acute relief of pain are not well tolerated
 - Titration not well suited to intermittent use, as seen with most chronic nociceptive pain
 - Titration is used with all currently available drugs for neuropathic pain

August 15, 2001

4

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ABBT311522

ABT-594 GPEC Review:

**Diabetic Neuropathic Pain Phase
IIb Study Results (M99-114)**

August 21, 2001

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Phase IIb Study in Neuropathic Pain (M99-114)

Study Results

- Summary
- Neuropathic pain reminder
- Study Design
- Efficacy Results
- Adverse Events
- Conclusions and Options

August 15, 2001

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M99-114 Neuropathic Pain

Summary

- **EFFICACY**
 - 150, 225 and 300 mcg BID are significantly better than placebo as measured by the primary efficacy variable (reduction in daily pain)

• ITT Analysis:	29-30%	vs. 17% placebo
– Gabapentin:	39%	vs. 22% placebo
• Completer Analysis:	38-48%	vs. 18% placebo
• Responder rates:	26% (ITT), 47% (Completer)	
 - Greater mean pain reduction and responder rates in site-based pain measurements
- **TOLERABILITY & SAFETY**
 - Dose dependent increase in nausea, vomiting, dizziness

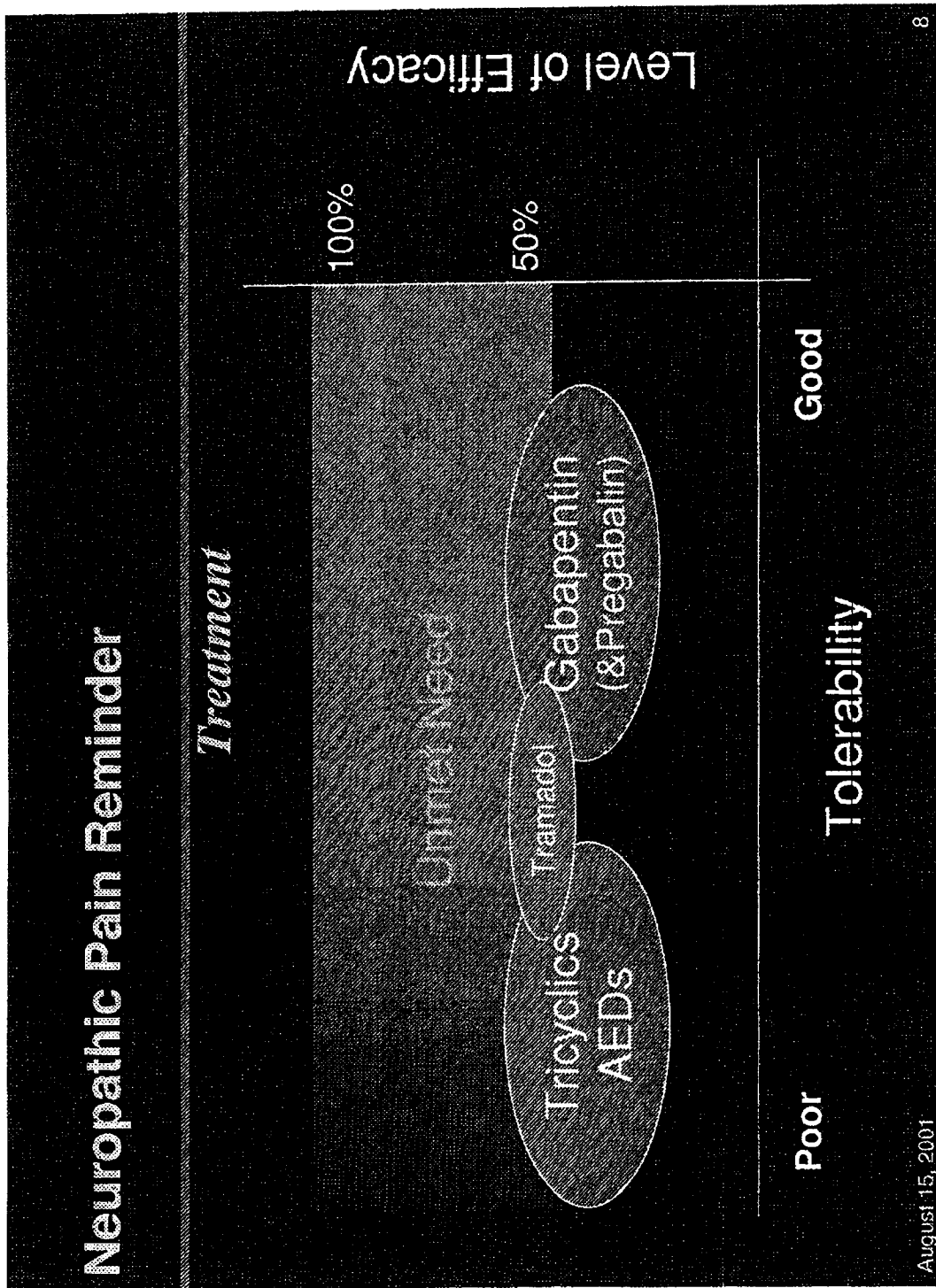
• Nausea:	34-46%	• Dizziness:	17-28%
• Vomiting:	15-21%	• Abnormal Dreams:	18-22%
 - Significant Discontinuation Rate: 66% due to AE at 300 mcg BID

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Neuropathic Pain Market

	2000 Rx (MM)	2000 sales (\$MM)	Rx CAGR (96-2000)	Sales CAGR (96-2000)
Total:				
US	10.6	\$470	6%	45%
Ex-US	18.1	\$235	11%	24%
Gabapentin				
US	3.9	\$352	80%	94%
Ex-US	1	\$42	125%	191%

Source: Decision Resources; IMS factored analysis.

- Growth of sales for neuropathic pain agents exceeds Rx growth:
 - Driven by continued growth of the branded and premium priced gabapentin (Neurontin), at the expense of other anti-epileptics and generic tricyclic antidepressants.

August 15, 2001

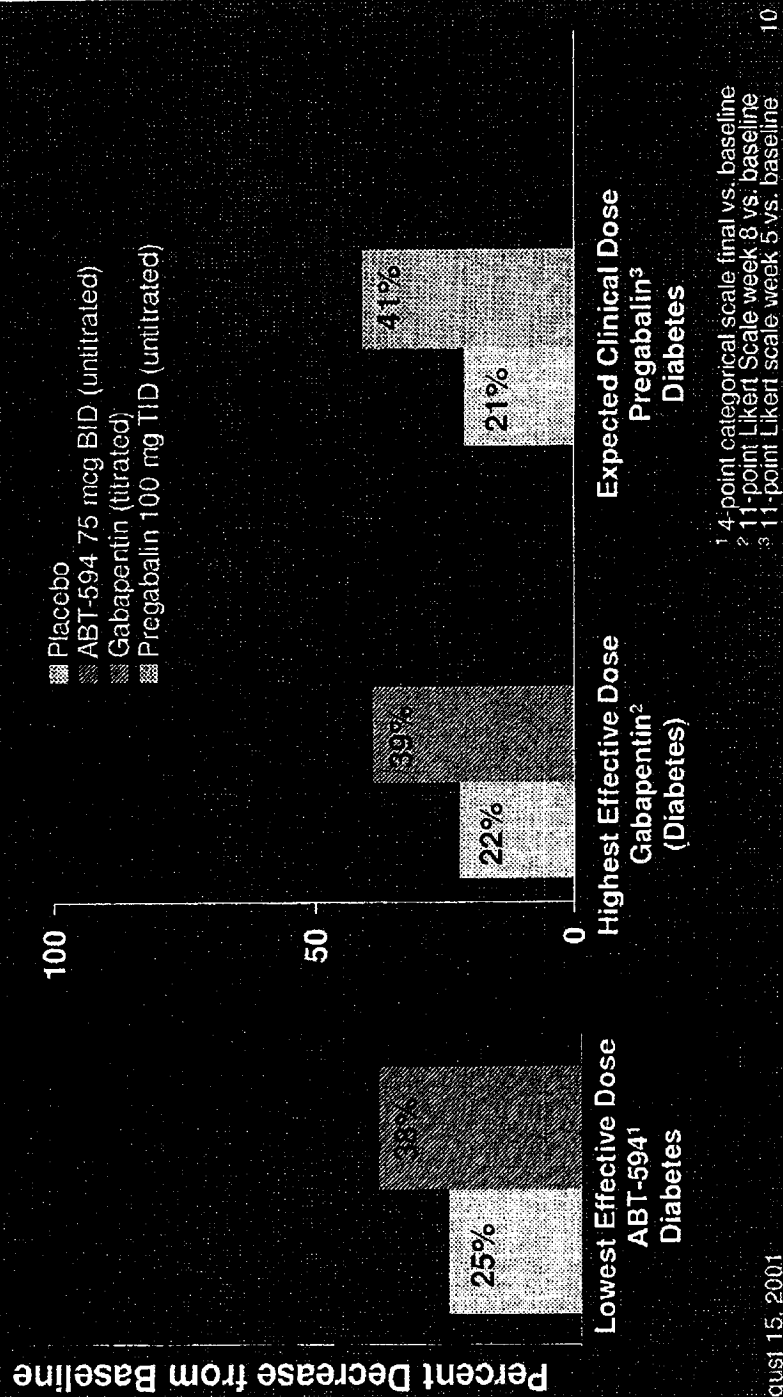
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Phase IIa: ABT-594 75 mcg BID Had a Similar Effect To Gabapentin

ABT-594 vs. Gabapentin and Pregabalin



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Phase IIa: ABT-594 75 mcg BID Untitrated Was Relatively Well Tolerated

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 ² 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

¹ Max, 1987 (n=29)

² M98-826 and M98-833 combined

N/A - Not Available

August 15, 2001

11

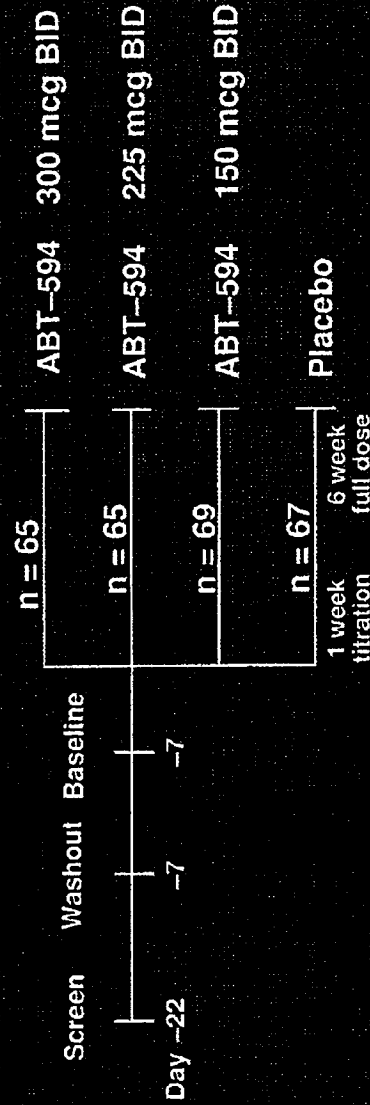
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ABBT311529

Phase IIb Neuropathic Pain (M99-114)

Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power
 - Planned: 80% for ES 0.46 with 80/group
 - Study: 60% for ES 0.46 with 50/group (ES 0.65 for site-based pain rating scale)
- Concomitant analgesics disallowed

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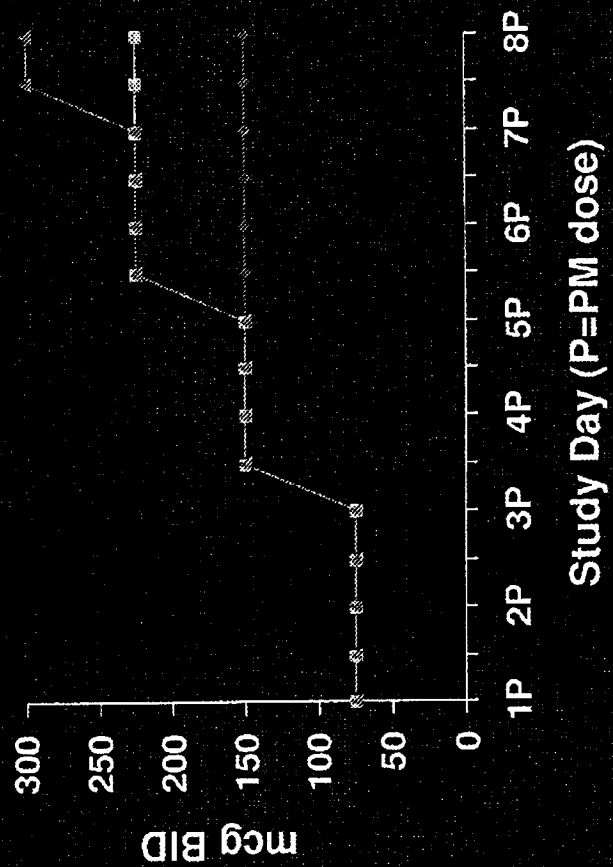
12

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ABBT311530

M99-114 Dose Titration Schedule

- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



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13

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ABBT311531

Premature Terminations Increased with Increasing doses of ABT-594

Subject Disposition

Reason for Discontinuation	Placebo	% of Subjects Discontinuing ABT-594		
		150 mcg BID	225 mcg BID	300 mcg BID
Adverse Event	9	28	46	66
Lack of Efficacy	9	9	3	7
Lost to Follow-up	0	0	1	3
Withdrew Consent	3	5	9	7
Other	2	2	4	3
Total Discontinuation	22	38	57	75

Percents may not sum correctly due to rounding

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14

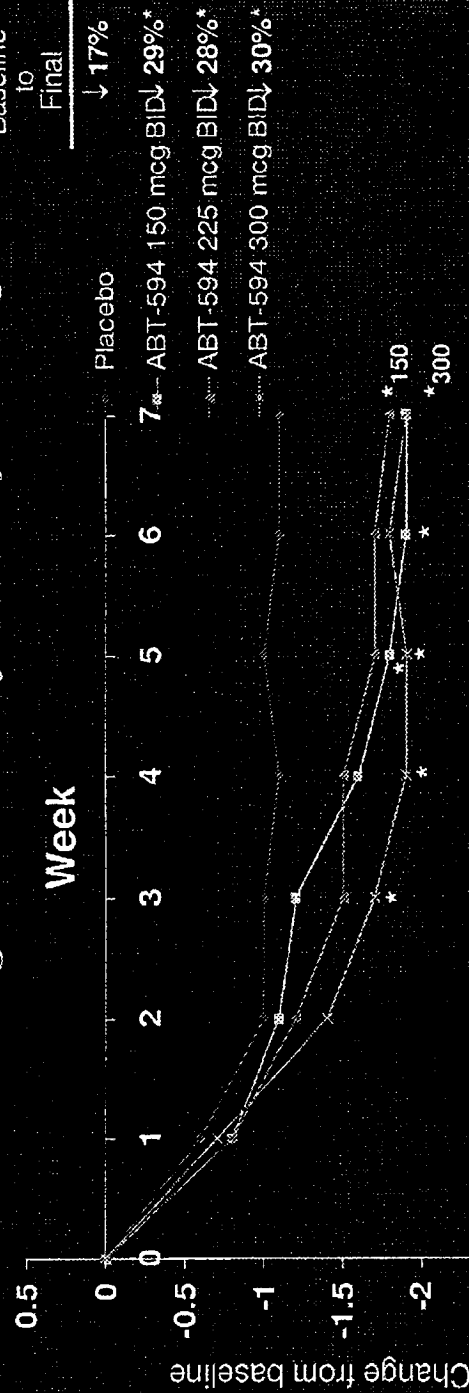
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ABBT311532

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: Intent to Treat Population

Pain Rating Scale-Diary (Weekly Average)

Change:
Baseline
to
Final



N% at week 7
Placebo 89%
ABT-594 150 mcg BID 86%
ABT-594 225 mcg BID 84%
ABT-594 300 mcg BID 79%

*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.6

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15

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ABBT311533

Completer Analysis May Predict Upside Potential of ABT-594

ITT

Scientific evaluation of
study results

Completer

Potential to predict
upside of efficacy if all
patients were able to
complete study

Advantages

Handicapped prediction
of upside potential of
efficacy given high
discontinuation rate
(especially early)

Disadvantages

Patients who completed
the Phase IIb study may
not predict accurately
efficacy if all patients
could tolerate ABT-594

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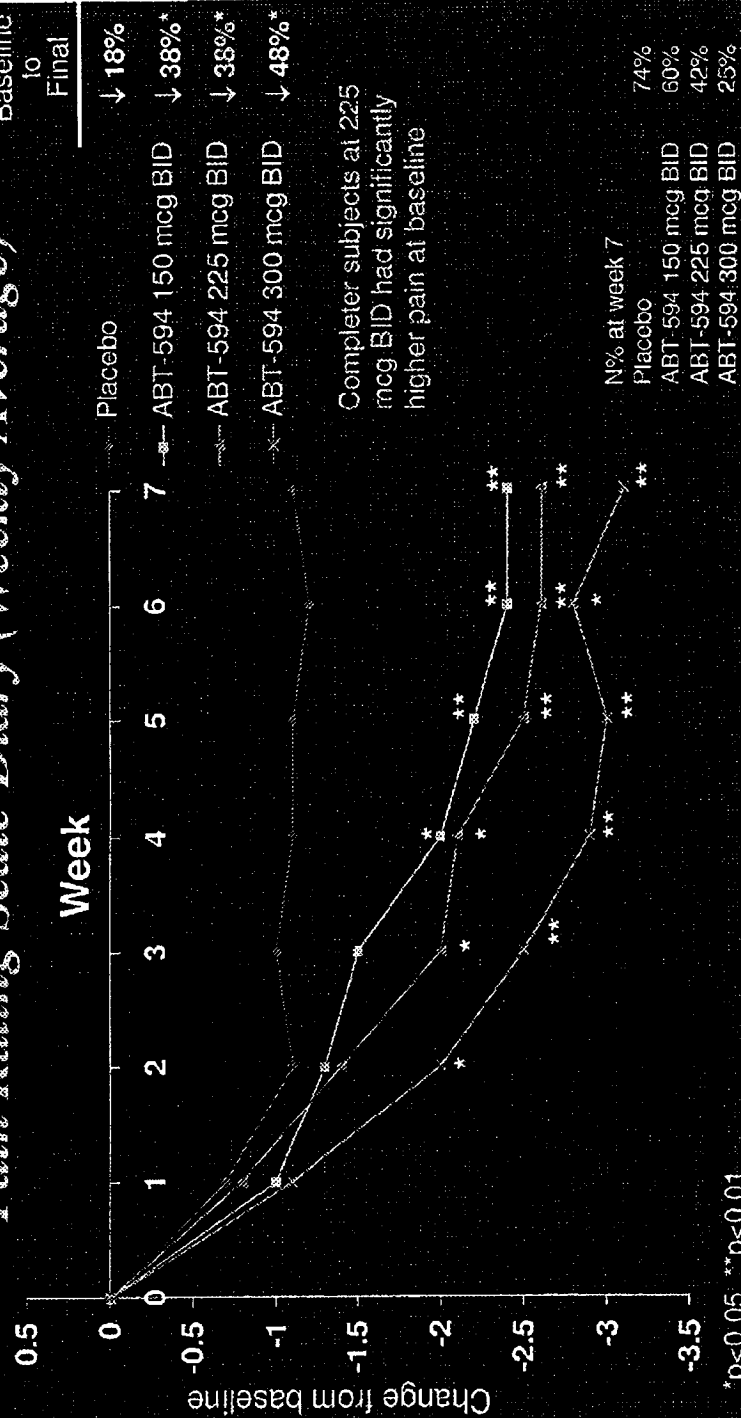
16

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ABBT311534

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: subjects who completed study

Pain Rating Scale-Diary (Weekly Average)



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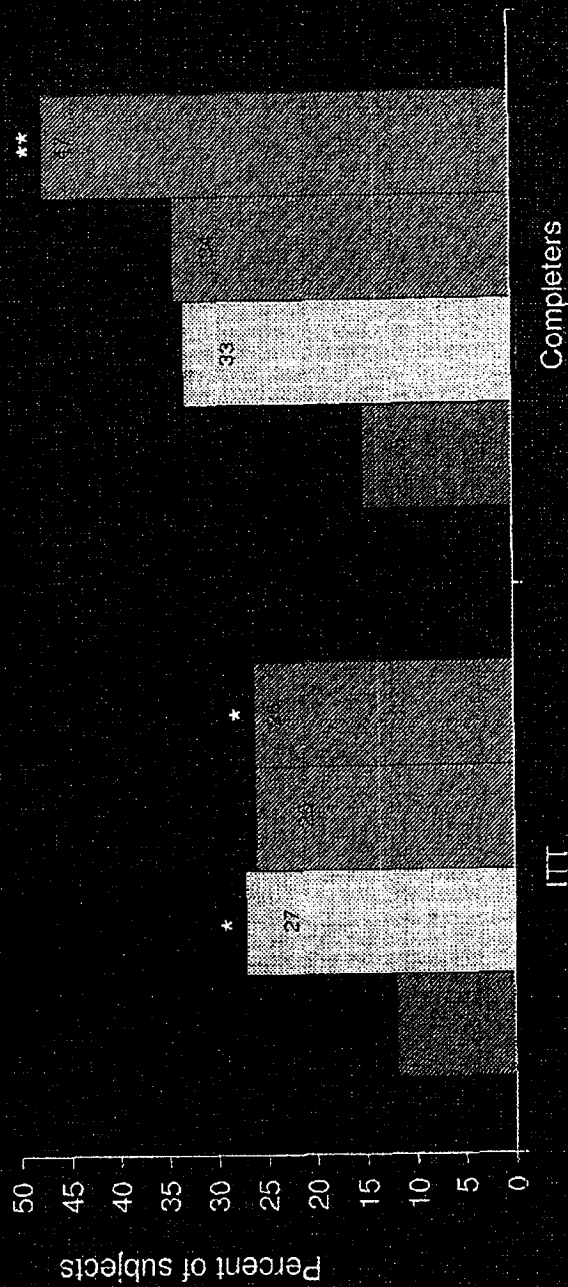
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ABBT311535

Responder Rates 50% or greater improvement

Pain Rating Scale-Diary

- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



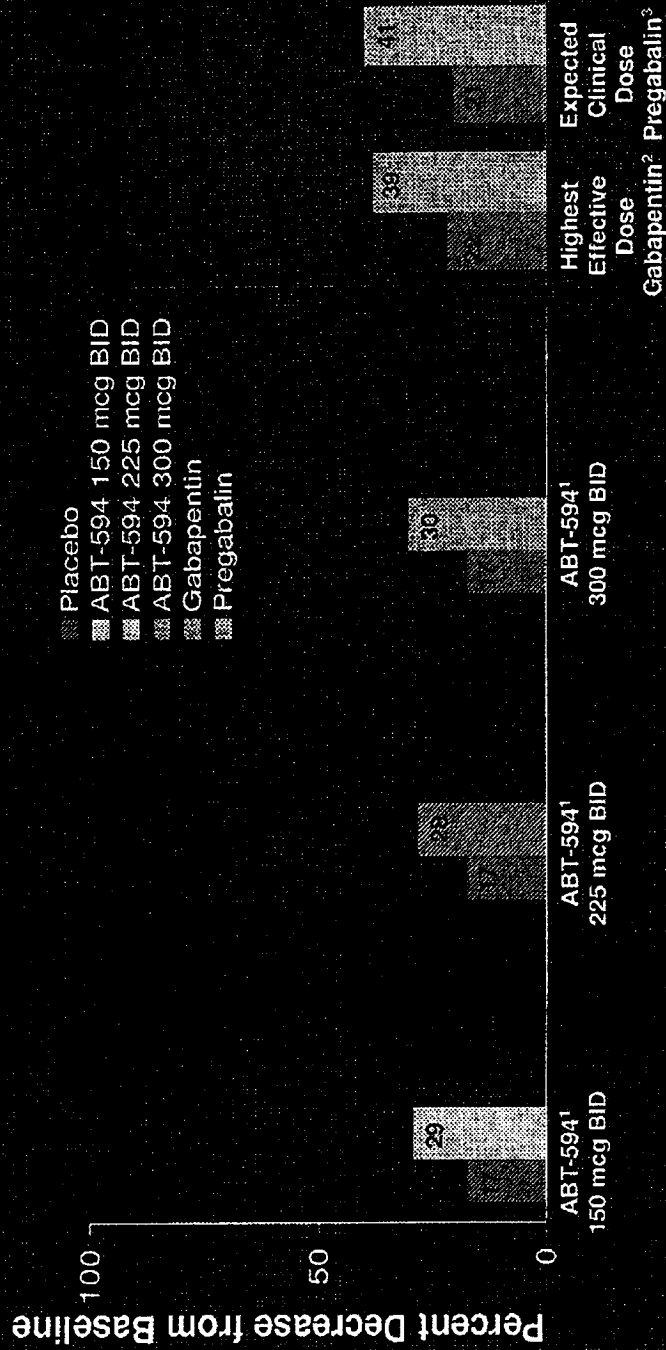
August 15, 2001 p<0.05, **p<0.01 vs. placebo

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ABT311536

ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain More than Gabapentin or Pregabalin

ABT-594 ITT vs. Gabapentin and Pregabalin



¹ 11-point Likert scale week 7 vs. baseline
² 11-point Likert scale week 8 vs. baseline
³ 11-point Likert scale week 5 vs. baseline

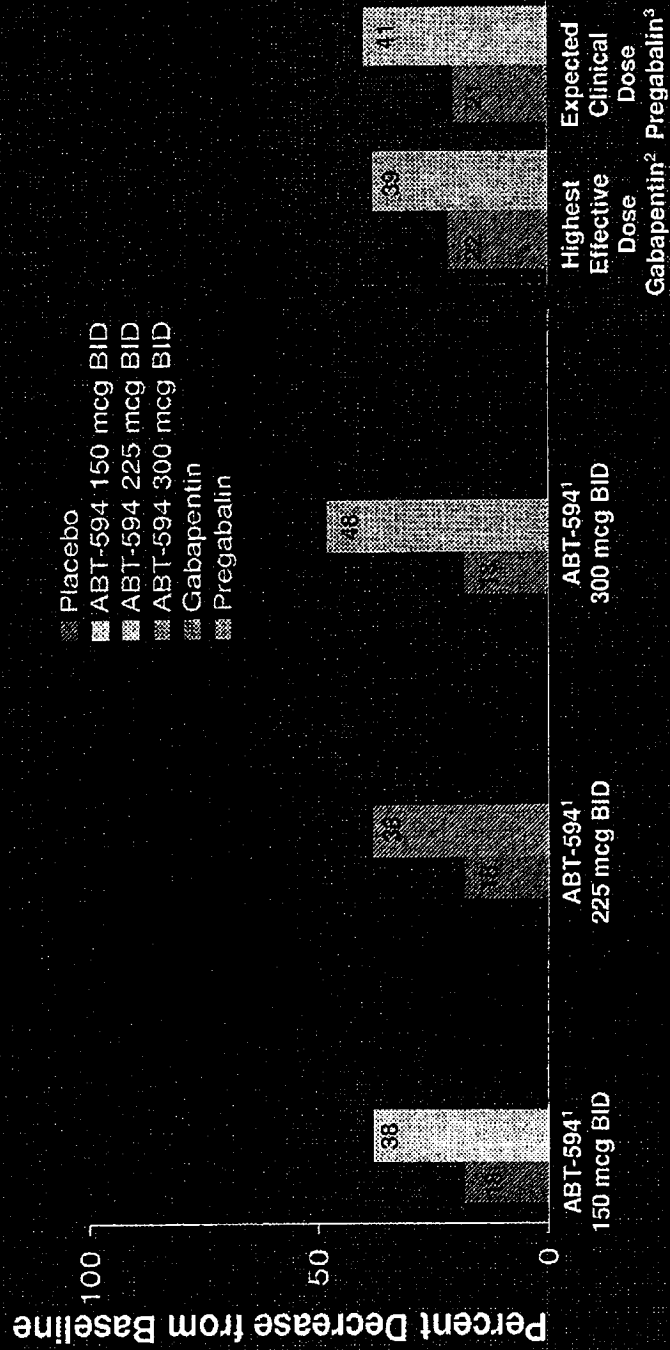
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ABBT311537

ABT-594 150, 225, 300 mcg BID May Reduce Diabetic Neuropathic Pain More than Gabapentin or Pregabalin

ABT-594 Completers vs. Gabapentin and Pregabalin



¹ 11-point Likert scale week 7 vs. baseline

² 11-point Likert scale week 8 vs. baseline

³ 11-point Likert scale week 5 vs. baseline

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ABBT311538

Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d ¹	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 150 mcg BID	ABT-594 300 mcg BID
Confusion	N/A	8%	5%	0%	1%
Somnolence	66%	23%	24%	2%	0%
Dizziness	28%	24%	27%	17%	28%
Nausea	N/A	8%	N/A	34%	46%
Vomiting	N/A	N/A	N/A	15%	21%
Peripheral edema	N/A	N/A	7%	0%	0%
Constipation	14%	N/A	N/A	3%	7%
Dry mouth	90%	N/A	N/A	3%	1%

¹ Max, 1987 (n=29)
N/A - Not Available

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21

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Efficacy and safety did not vary meaningfully by subject characteristics

- Smoker/Non-smoker
- Male/Female
- Weight
- Age
- Renal Function

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22

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ABBT311540

ABT-594 150, 225 and 300 mcg BID Were Not Associated with Clinically
Meaningful Changes in Vital Signs, ECGs or Laboratory Data

- Vital signs
- ECG
- Laboratory data

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23

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ABBT311541

McCarthy Deposition Exhibit 54

D's Exhibit 661

Part 2

M99-114: Neuropathic Pain

Conclusions

- ABT-594 significantly reduces diabetic neuropathic pain
- ABT-594, as administered without additional improvements in tolerability, has a narrow therapeutic window
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

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24

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ABBT311542

ABT-594 Options

- A: Attempt tolerability improvement with ABT-594
 - Explore more prolonged titration
 - Co-administer anti-emetic
 - Protocol Ready
 - 7, 11, 21 day titrations
 - Co-administered anti-emetic
 - Detailed assessments of adverse events
 - \$2.8 MM Fully burdened ~~VERIFY~~
- B: No additional experiments with ABT-594
- Subtype selective NNR for pain back-up

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25

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ABBT311543

Rationale for Titration and/or co-administration of an anti-emetic to improve tolerability of ABT-594

- Titration
 - General hypotheses
 - Adverse event tolerance
 - Homeostasis
 - Evidence
 - Attenuation of AEs over time in earlier studies, especially doses ≤ 75 mcg BID
 - Preclinical evidence of attenuation over time
 - Titration is used to improve the tolerability of most analgesic, neurological and psychiatric Drugs
- Anti-emetic
 - Suppression of priming effect during tolerance/homeostasis
 - Preclinical studies
 - Dopamine antagonists
 - 5-HT₃ antagonists

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26

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ABBT311544

M99-114 Study Review

Back-up

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ABBT311545

M99-114: Neuropathic Pain

Outcome Measures

- **Primary**
 - Weekly average of daily Pain Rating Scale (11-point Likert in a diary)
 - Change from baseline to last 7 days on drug
- **Secondary**
 - Site-based Pain Rating Scale (11-point Likert)
 - Neuropathic Pain Scale
 - Patient Global Impression of Change
 - Clinician Global Impression of Change
 - SF-36

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28

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ABBT311546

M99-114: Neuropathic Pain

Outcome Measures

- **Pain Rating Scale**

PRIMARY

0	1	2	3	4	5	6	7	8	9	10
no pain								worst pain possible		

- **Neuropathic Pain Scale (NPS)**

— 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp										The most sharp sensation imaginable (like a knife)									
1	2	3	4	5	6	7	8	9	10										

- **Subject, Clinician Impression of Change**

1	Much Improved
2	Moderately Improved
3	Minimally Improved
4	No Change
5	Minimally Worse
6	Moderately Worse
7	Much Worse

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29

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ABBT311547

Opinion Leader Comments on ABT-594 Results

- Russ Portenoy
- Howard Fields
- Martin Koltzenburg

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30

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ABBT311548

ABT-594 Tolerability Improvement Study

- Controlled, randomized, double-blind, placebo-controlled Phase I
- Adequately powered
- Five Groups:
 - Placebo
 - 7 Day titration \pm anti-emetic up through steady state
 - 11 Day titration
 - 24 Day titration

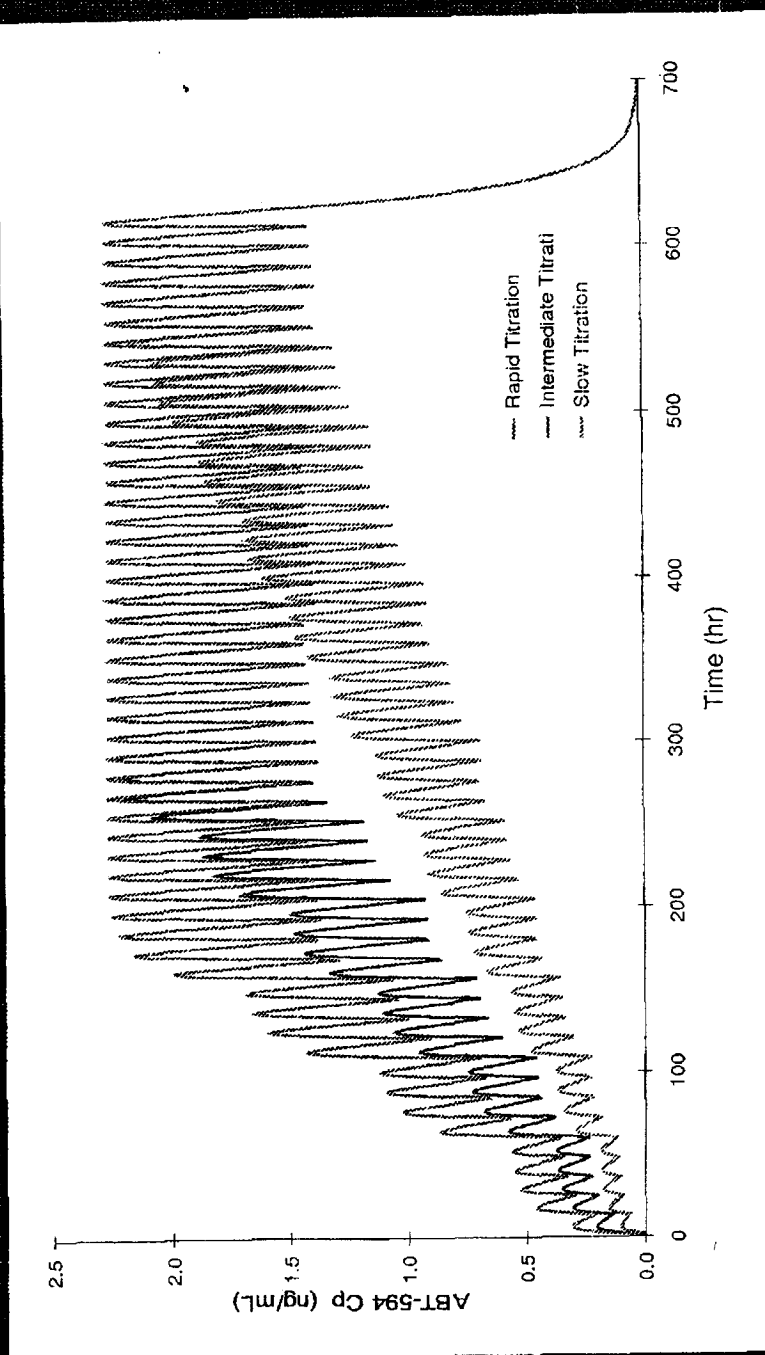
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31

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ABBT311549

ABT-594 Tolerability Improvement Study



32

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ABBT311550

Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological and Psychiatric Drugs

Tramadol in naïve patients: Ruoff Study

	1 Day to 200 mg/day n=130	4 Days to 200 mg/day n=129	10 Days to 200 mg/day n=132
Nausea	29%	31%	21%
Vomiting	10%	12%	8%
Dizziness	24%	19%	8%
Discontinuation Due to AEs	31%	24%	15%

- Patients with chronic joint pain treated with daily NSAIDs and requiring additional pain relief.

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33

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ABBT311551

Titration Is Used to Improve the Tolerability of Most Analgesic, Neurological, and Psychiatric Drugs

Tramadol in intolerant patients: Petrone Study

	10 Days to 200 mg/day n=54	16 Days to 200 mg/day n=59	13 Days to 150 mg/day n=54
Nausea	54%	42%	33%
Vomiting	19%	12%	7%
Dizziness	7%	7%	7%
Discontinuation Due to AEs	54%	34%	30%

- Patients who had discontinued due to nausea or vomiting during a rapid escalation of tramadol dose (4 days to 200 mg/day) were enrolled in the titration evaluation.
- Patients with chronic pain treated with daily NSAIDs.

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34

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ABBT311552

Hypotheses for ABT-594-induced Emesis

- Parenteral administration also elicits emesis in preclinical studies
- No models exist to determine the relative contribution of central and peripheral actions of ABT-594 in emesis

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35

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ABBT311553

ABT-594 Parenteral

- An option to evaluate different rates-of-rise under single dose administration
- Additional preclinical experiments required
 - More fully explore safety of different rates-of-rise
 - Parenteral drug safety studies
- Formulation development
- Time & Cost
 - EST 6 months
 - EST \$ 0.5 MM

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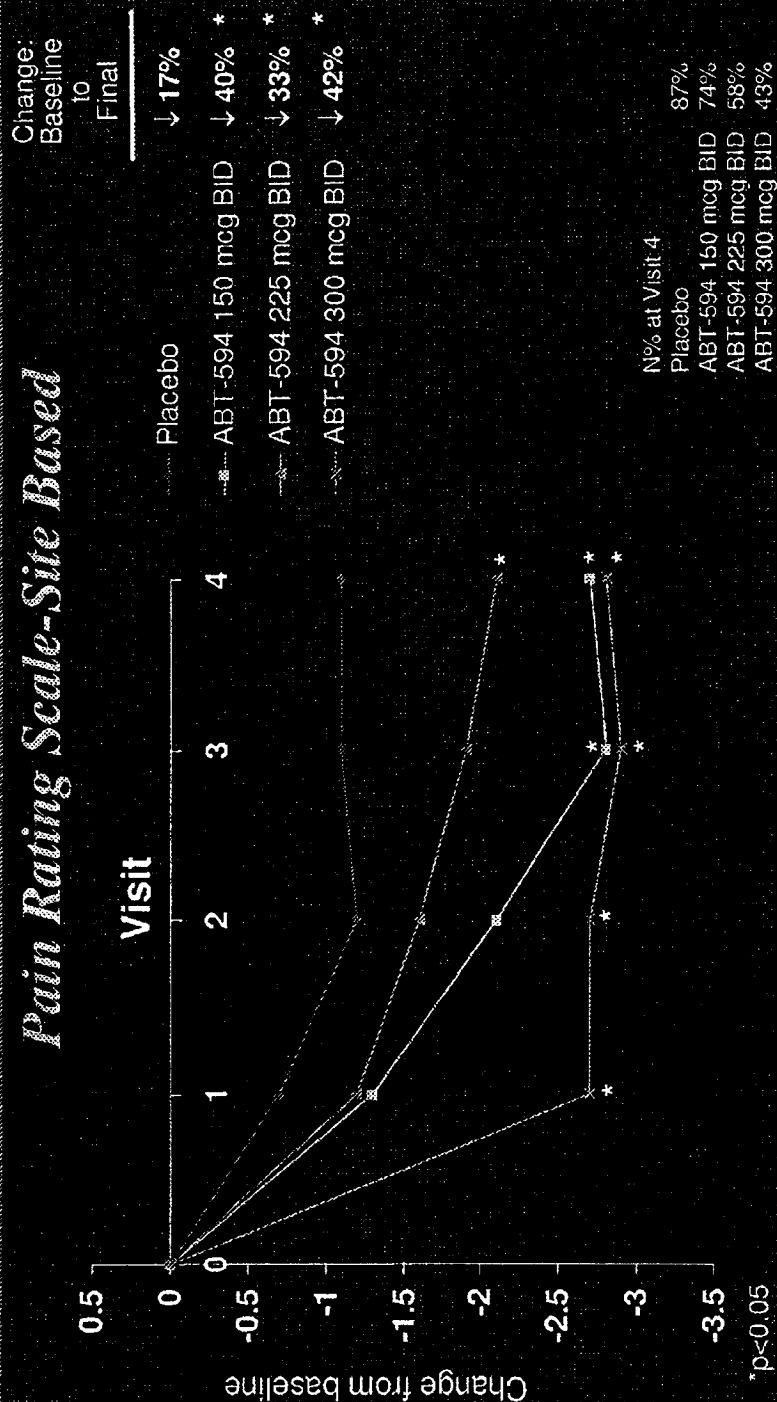
36

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ABBT311554

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: Intent to Treat Population

Pain Rating Scale-Site Based



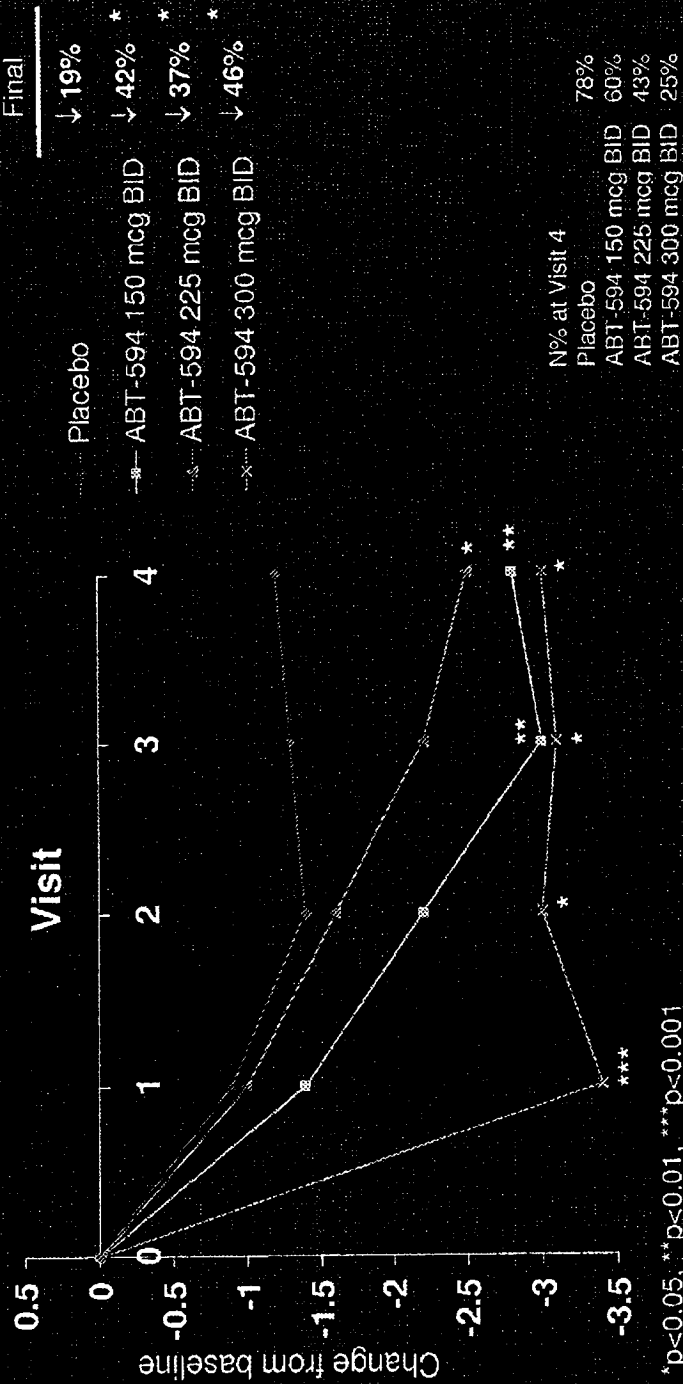
37

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ABT311555

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: subjects who completed study

Pain Rating Scale-Site Based



38

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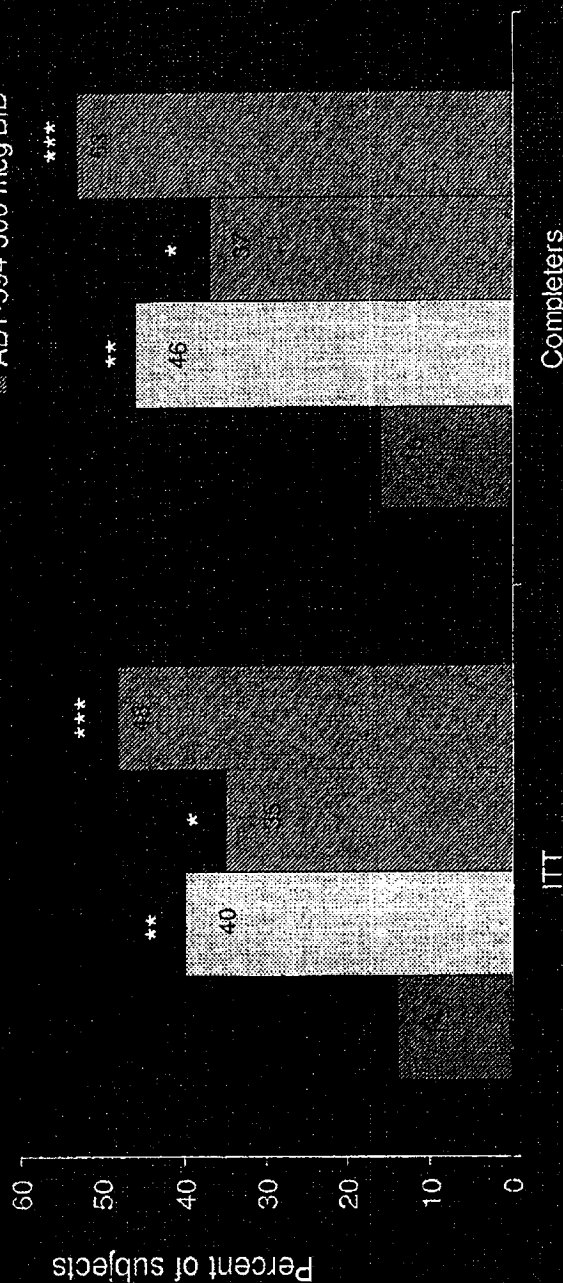
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ABBT311556

Responder Rates 50% or greater improvement

Pain Rating Scale-Site

- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



August 15, 2001 *p<0.05, **p<0.01, ***p<0.001 vs. placebo

39

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ABBT311557

M99-114 Neuropathic Pain

Summary

- **Initial Questions**
 - Where do doses evaluated to date fit on the dose-response curve?
 - PK/PD effect?
 - Can tolerability be improved?
 - Differentiation of patient populations
 - Dosage administration
 - If tolerability is improved, will there be even more efficacy?
 - How much will patients benefit from ABT-594?
 - If administered as in M99-114
 - Given hypothetical improvements in tolerability & efficacy
- **Conclusions**
 - ABT-594 significantly reduces diabetic neuropathic pain
 - ABT-594, as administered without any optimization, has a narrow therapeutic window
 - ABT-594 has the potential to be an important treatment for neuropathic pain; additional analyses will evaluate the probability that differentiation of patient populations or changes in dosage administration can improve therapeutic index

40

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ABBT311558

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ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT

- *Independent of future business decisions regarding ABT-594...*

- ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
- NNRs are now fully validated as a viable mechanism to treat neuropathic pain
- For the first time in decades there is now an additional class of analgesic agents:

- **NNRs**
- OPIOIDS
- NSAIDs/COX-2s
- ACETAMINOPHEN
- TCAs/AEDs

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41

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ABBT311559

Treatment Groups Were Similar in Terms of Demographics at Baseline

M99-114 Baseline Characteristics

		All Patients (N=266)
Gender	Female	45%
	Male	55%
Race	White	89%
	Black	9%
Age	Mean	62
	Range	20-86
Weight	Mean	202
	Range	112-278
Nicotine Use	Former	36%
	Never	53%
	Current	11%

42

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ABBT311560

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Treatment Groups Were Similar in Terms Pain at Baseline

M99-114 Baseline Characteristics

	Placebo	ABT-594 150 mcg BID	ABT-594 225 mcg BID	ABT-594 300 mcg BID
Pain Rating Scale Diary (10)	6.5	6.6	6.7	6.7
Pain Rating Scale Site (10)	6.5	6.7	6.7	6.9
Neuropathic Pain Scale (100)	56.5	55.1	56.3	57.3

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43

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ABBT311561

Premature Termination Increased with Increasing Doses of ABT-594

M99-114 DAYS TO PREMATURE DISCONTINUATION



Product 8 Study Code: M99-114; Title: Phase 3 Study of ABT-594 in Patients with Multiple Myeloma; Date: 11/14/00; Version: 1.0

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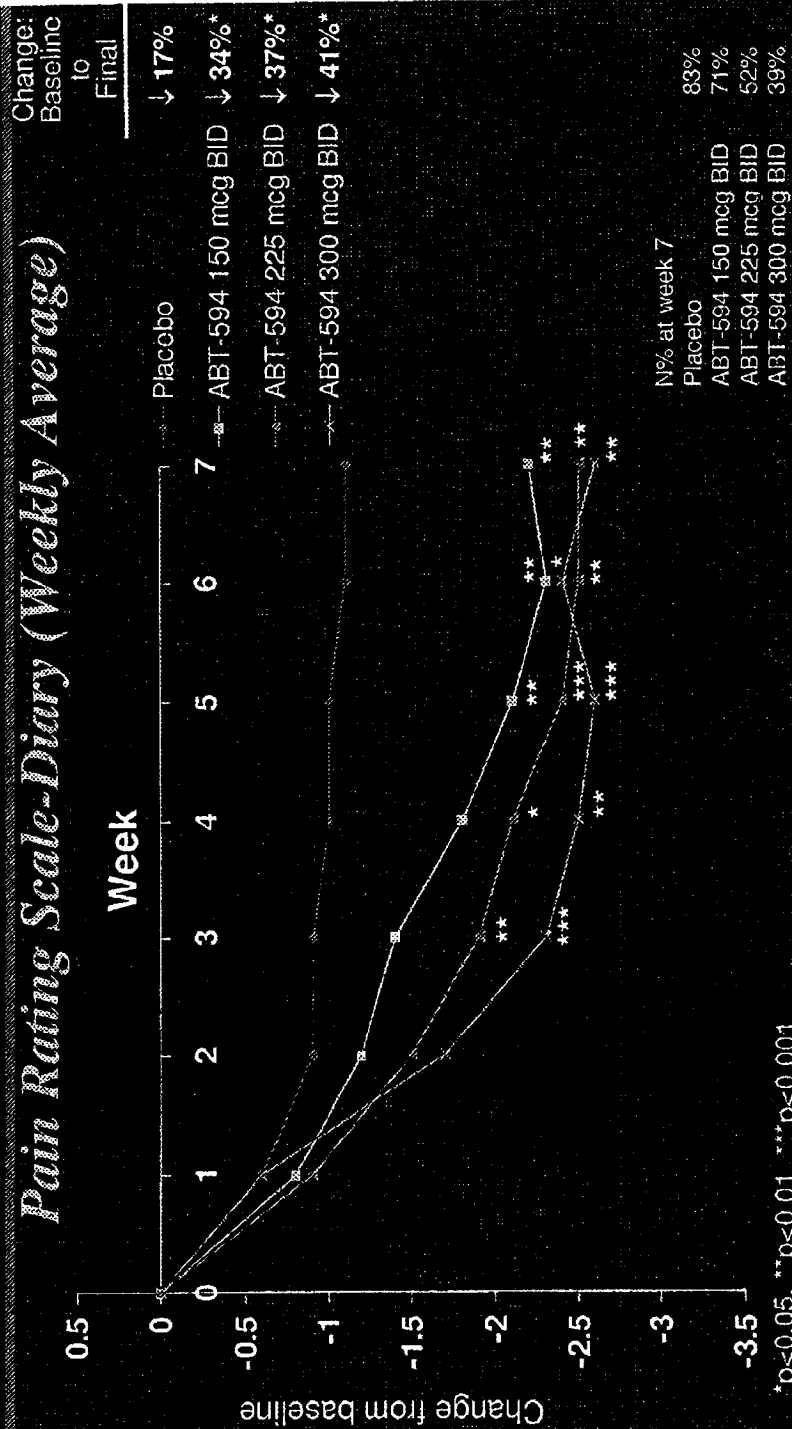
44

ABBT311562

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ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by the Primary Efficacy Variable: subjects who complete at least 21 days

Pain Rating Scale-Diary (Weekly Average)



45

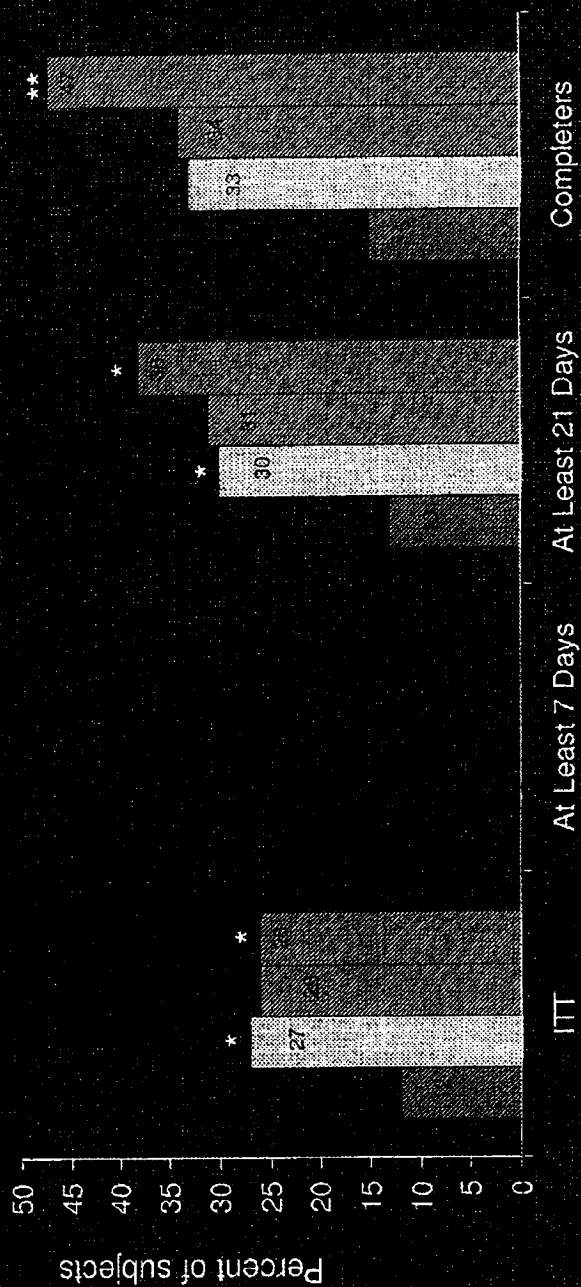
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ABBT311563

Responder Rates 50% or greater improvement

Pain Rating Scale-Diary

- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID

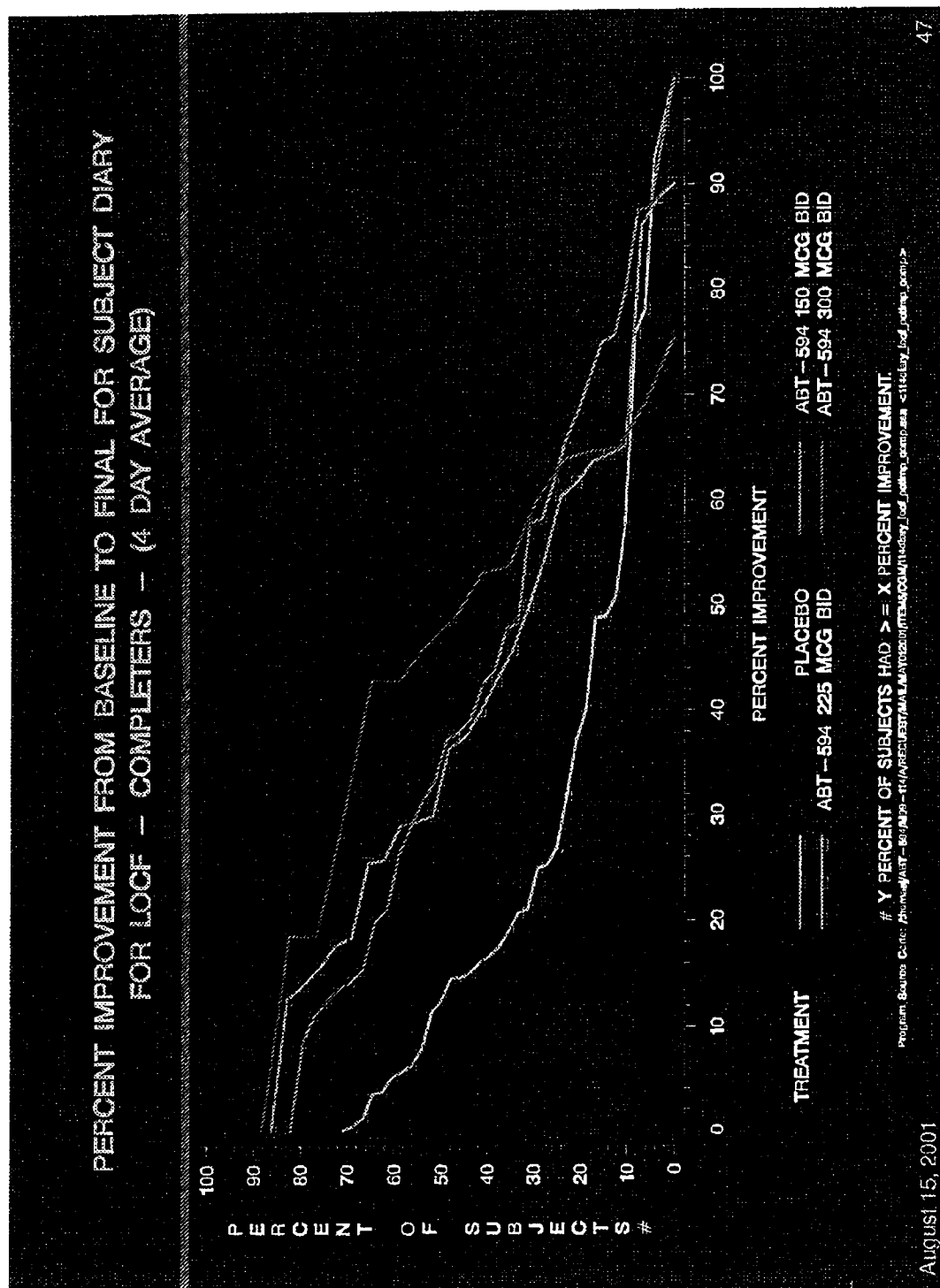


August 15, 2001 p<0.05

46

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ABBT311564



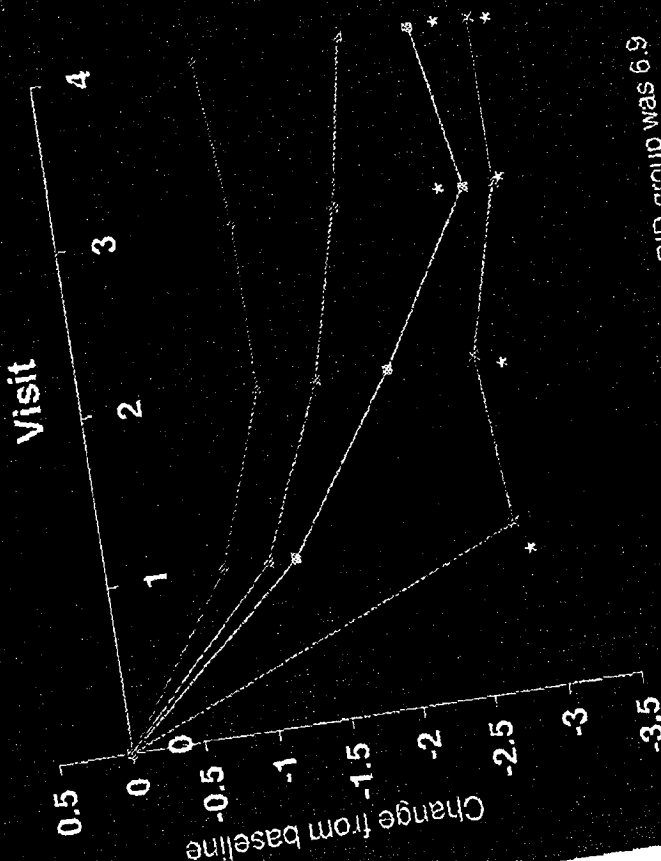
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ABB T311565

ABBT311566

ABT-594 150, 225, & 300 mcg BID Reduced Pain Significantly vs. Placebo as Measured by Site-Based Pain Rating Scale: subjects who complete at least 21 days

Pain Rating Scale (Site Based)



$p < 0.05$

Maximum possible decrease for 300 mcg BID group was 6.9

August 15, 2001

Change: Baseline to Final	
↓ 17%	Placebo
↓ 40%	ABT-594 150 mcg BID
↓ 32%	ABT-594 225 mcg BID
↓ 42%	ABT-594 300 mcg BID

N% at Visit 4	
77%	Placebo
77%	ABT-594 150 mcg BID
77%	ABT-594 225 mcg BID
77%	ABT-594 300 mcg BID

43

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McCarthy Deposition Exhibit 54

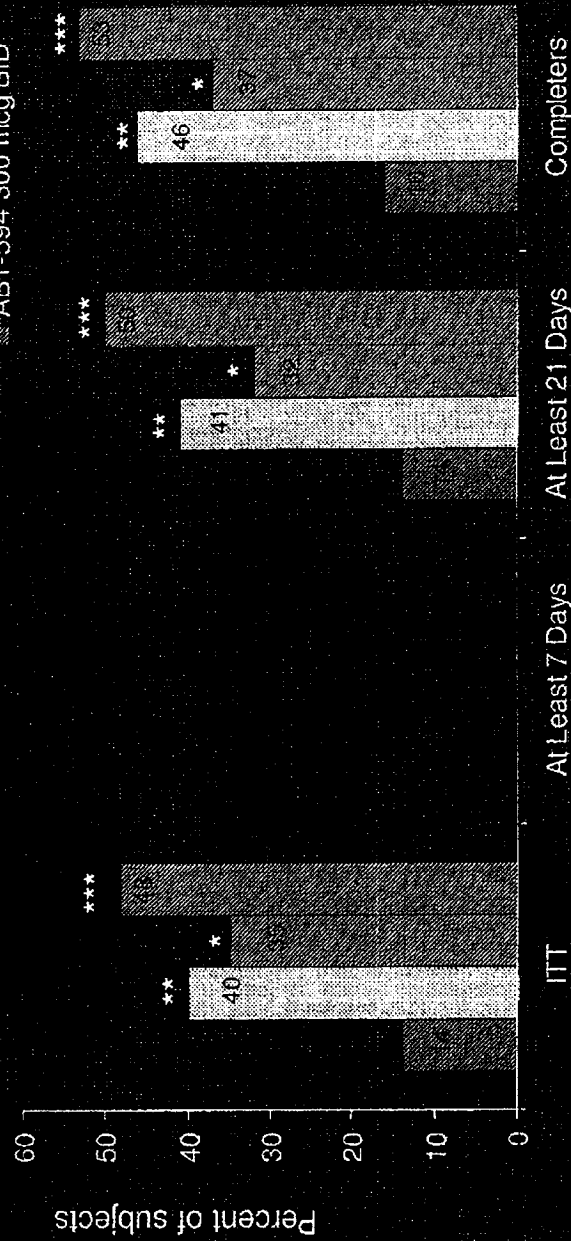
D's Exhibit 661

Part 3

Responder Rates 50% or greater improvement

Pain Rating Scale-Site

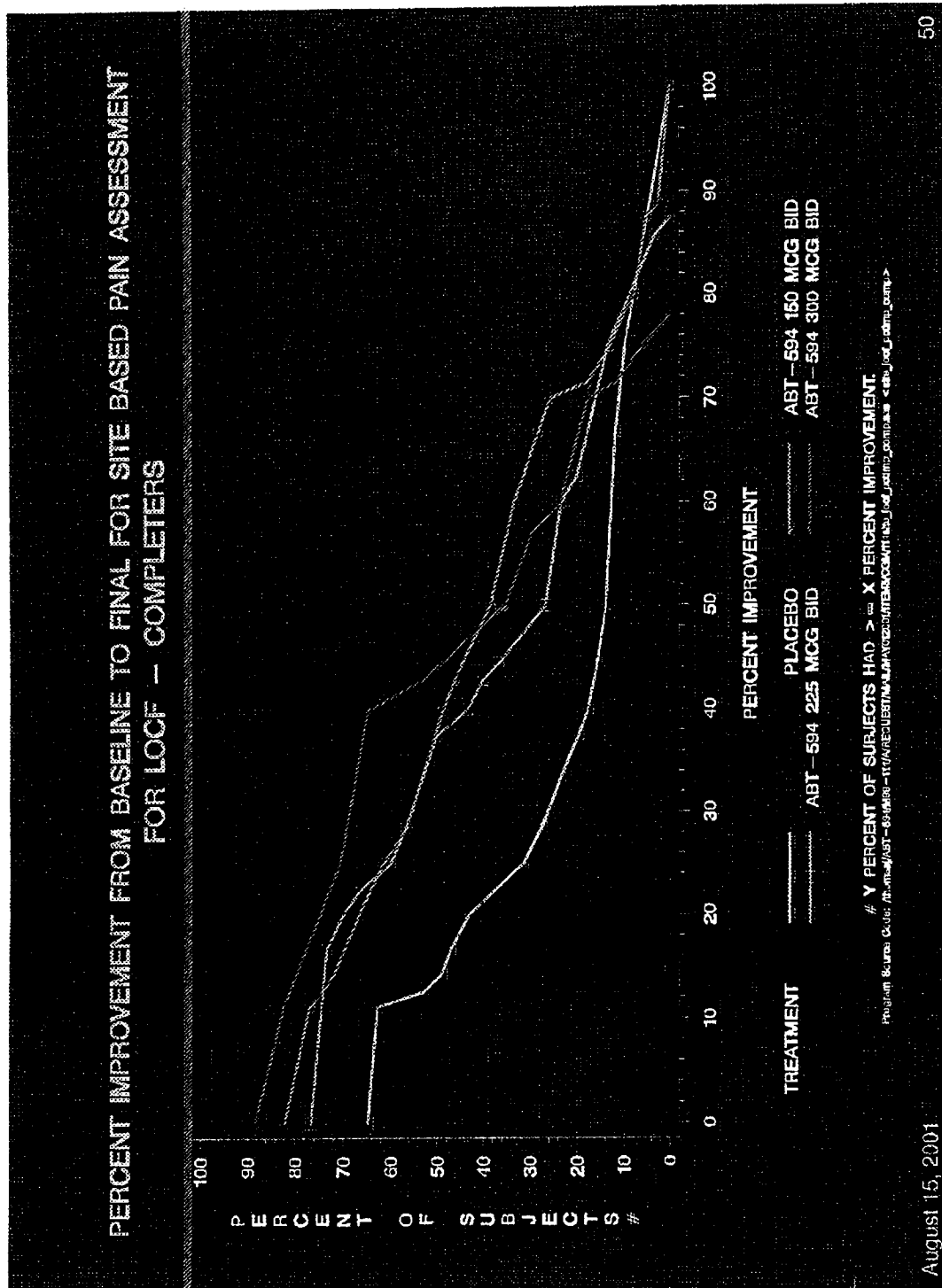
- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



August 15, 2001 ***p<0.05, **p<0.01, *p<0.001 vs. placebo

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ABT311567

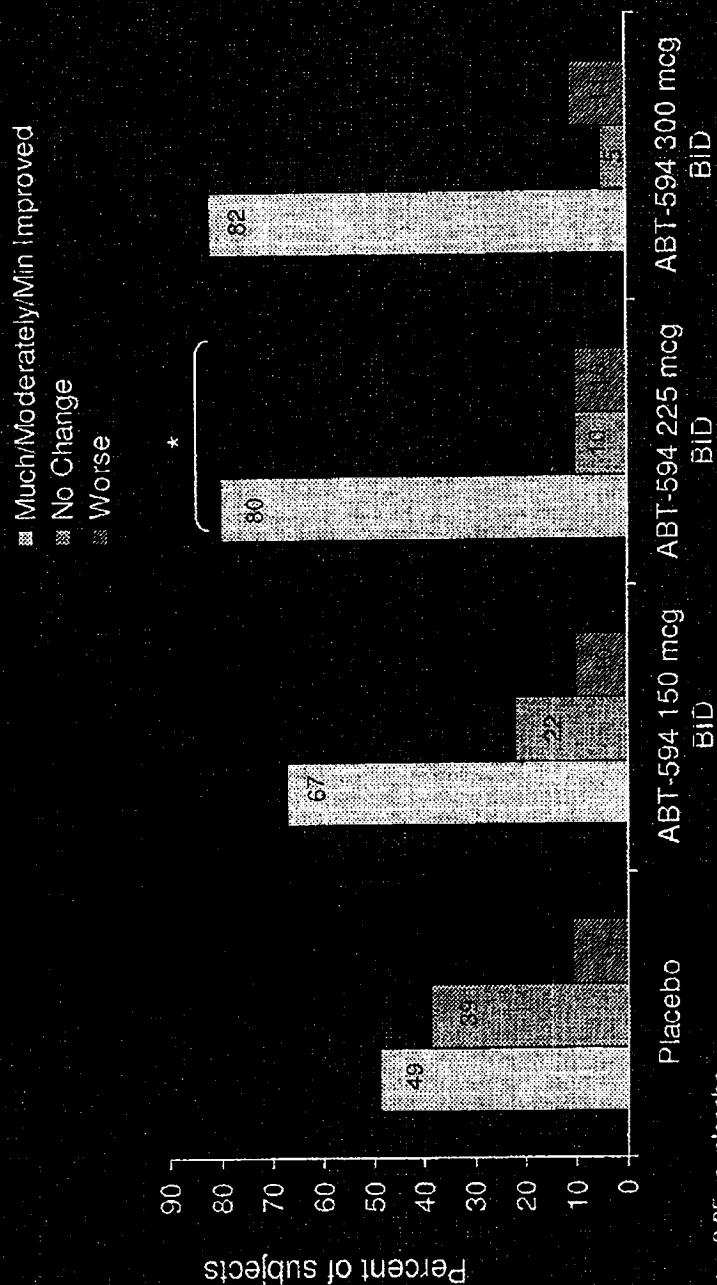


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ABB T311568

ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the SUBJECT Global Impression of Change: Subjects Who Completed Study

SGIC



51

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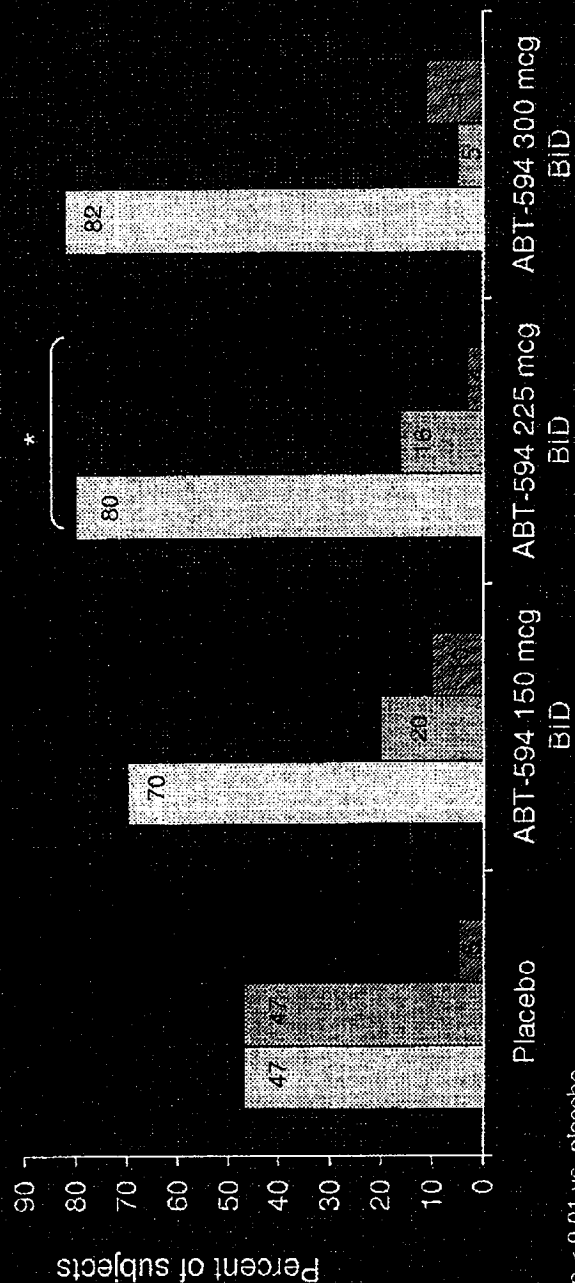
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ABBT311569

ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the CLINICIAN Global Impression of Change: Subjects Who Completed Study

CGIC

■ Much/Moderately/Min Improved
 ■ No Change
 ■ Worse



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52

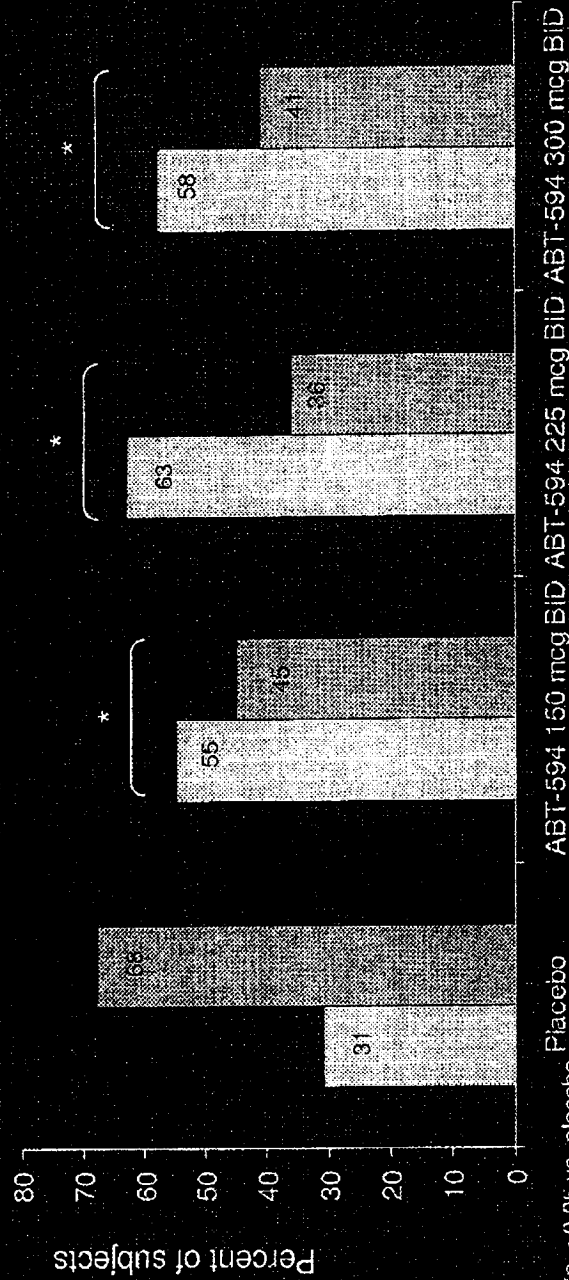
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ABBT311570

ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the SUBJECT Global Impression of Change: Subjects Who Completed Study

SGIC

- Much or Moderately Improved
- ▨ Minimally Improved, No Change or Worsened



*p < 0.05 vs. placebo

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53

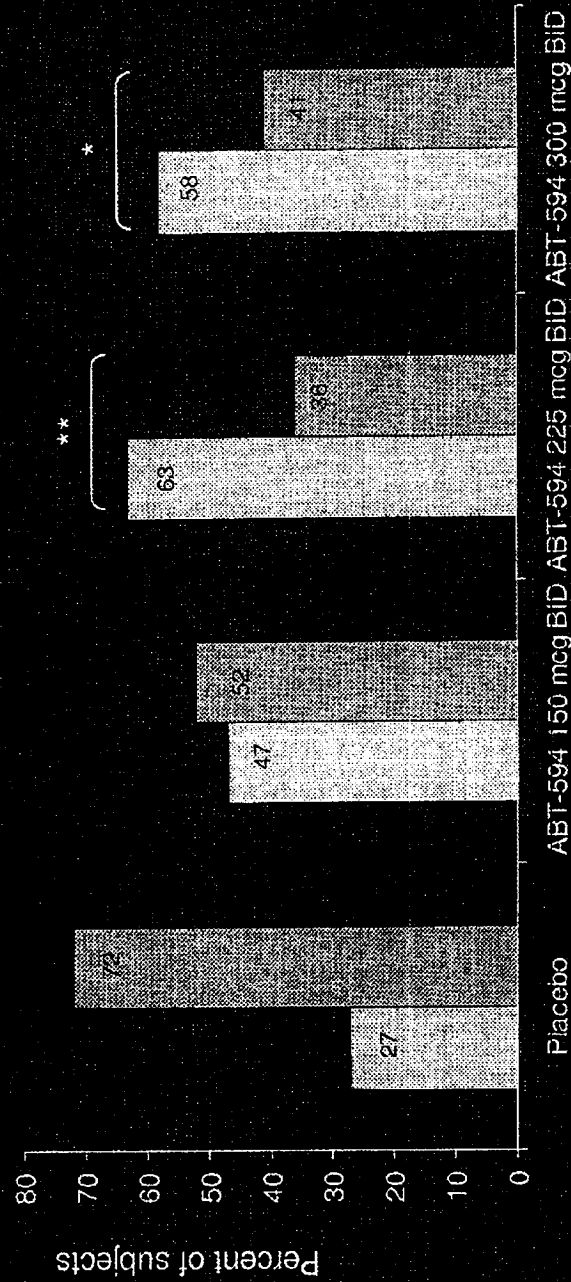
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ABBT311571

ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the CLINICIAN Global Impression of Change: Subjects Who Completed Study

CGIC

- Much or Moderately Improved
- Minimally Improved, No Change or Worsened



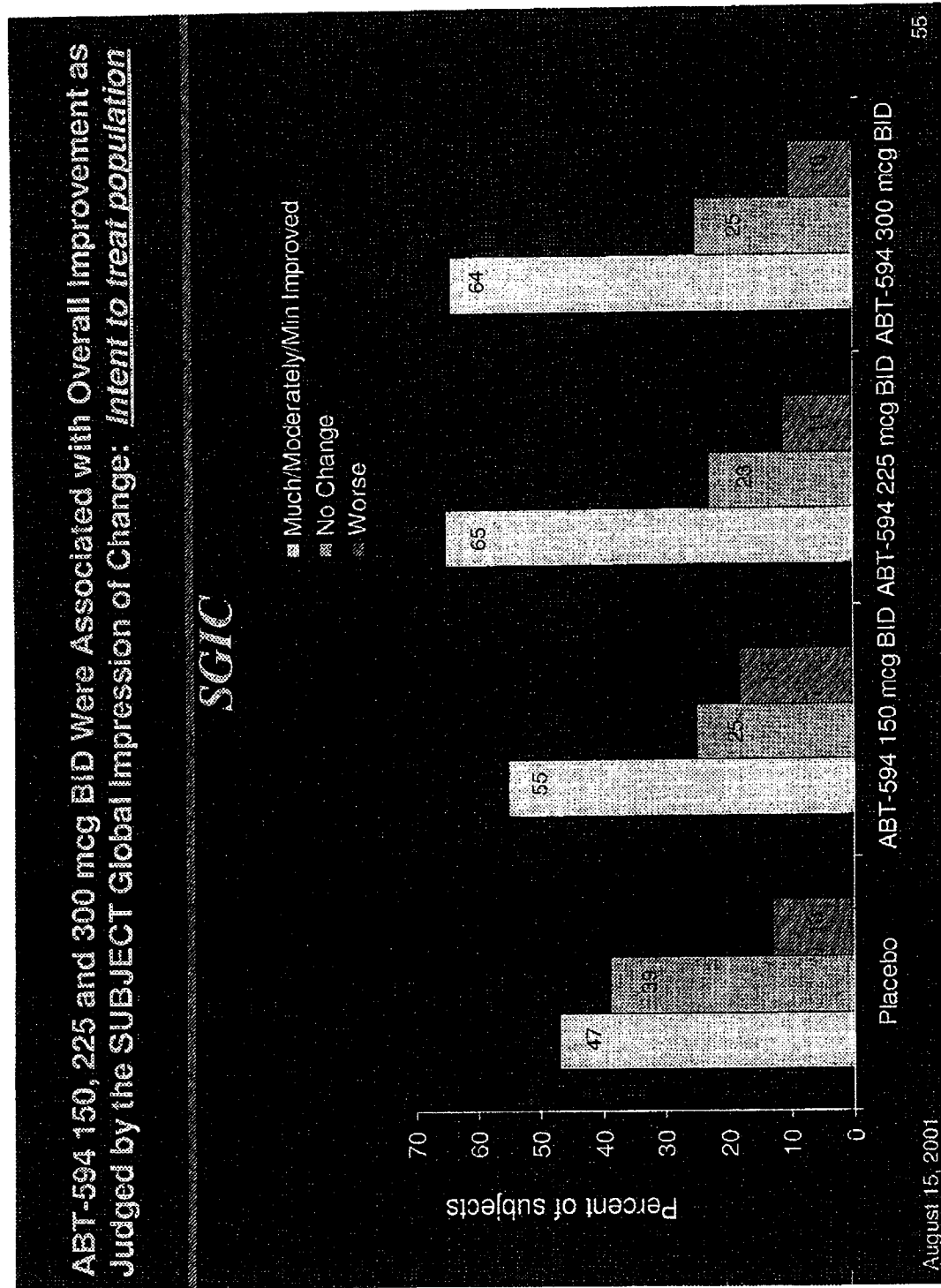
*p < 0.05, ** p < 0.01 vs. placebo

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54

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ABBT311572



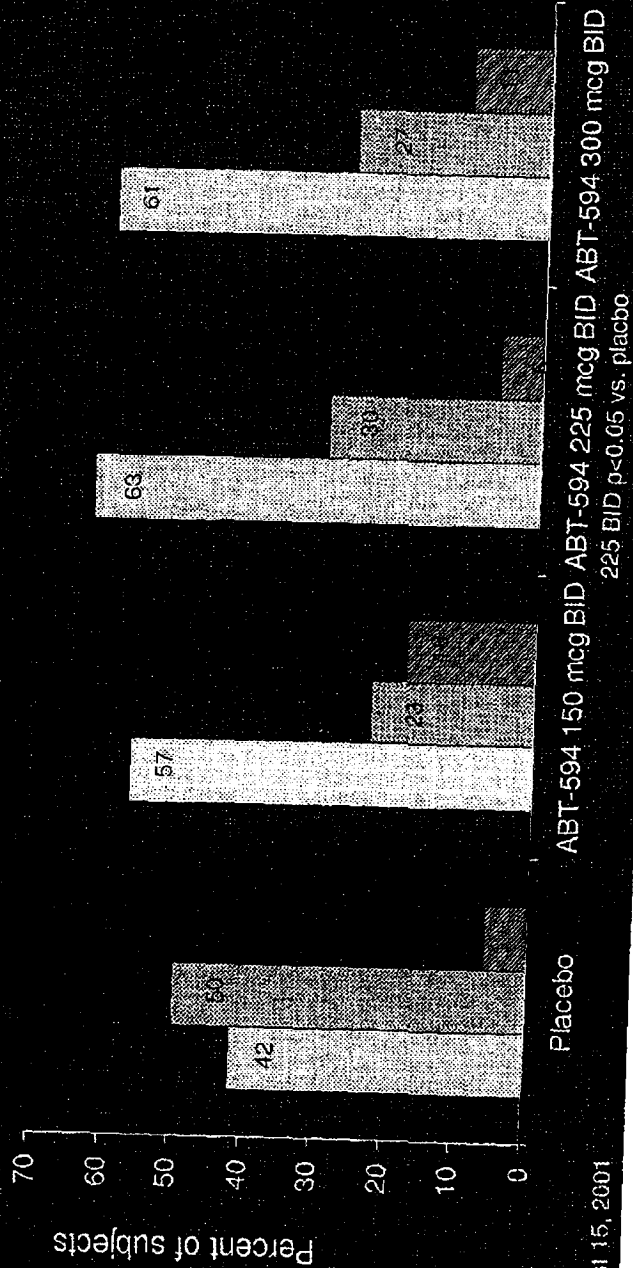
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ABBT311573

ABT-594 150, 225 and 300 mcg BID Were Associated with Overall Improvement as Judged by the CLINICIAN Global Impression of Change: *Intent to treat population*

CGIC

■ Much/Moderately/Min Improved
 ■ No Change
 ■ Worse

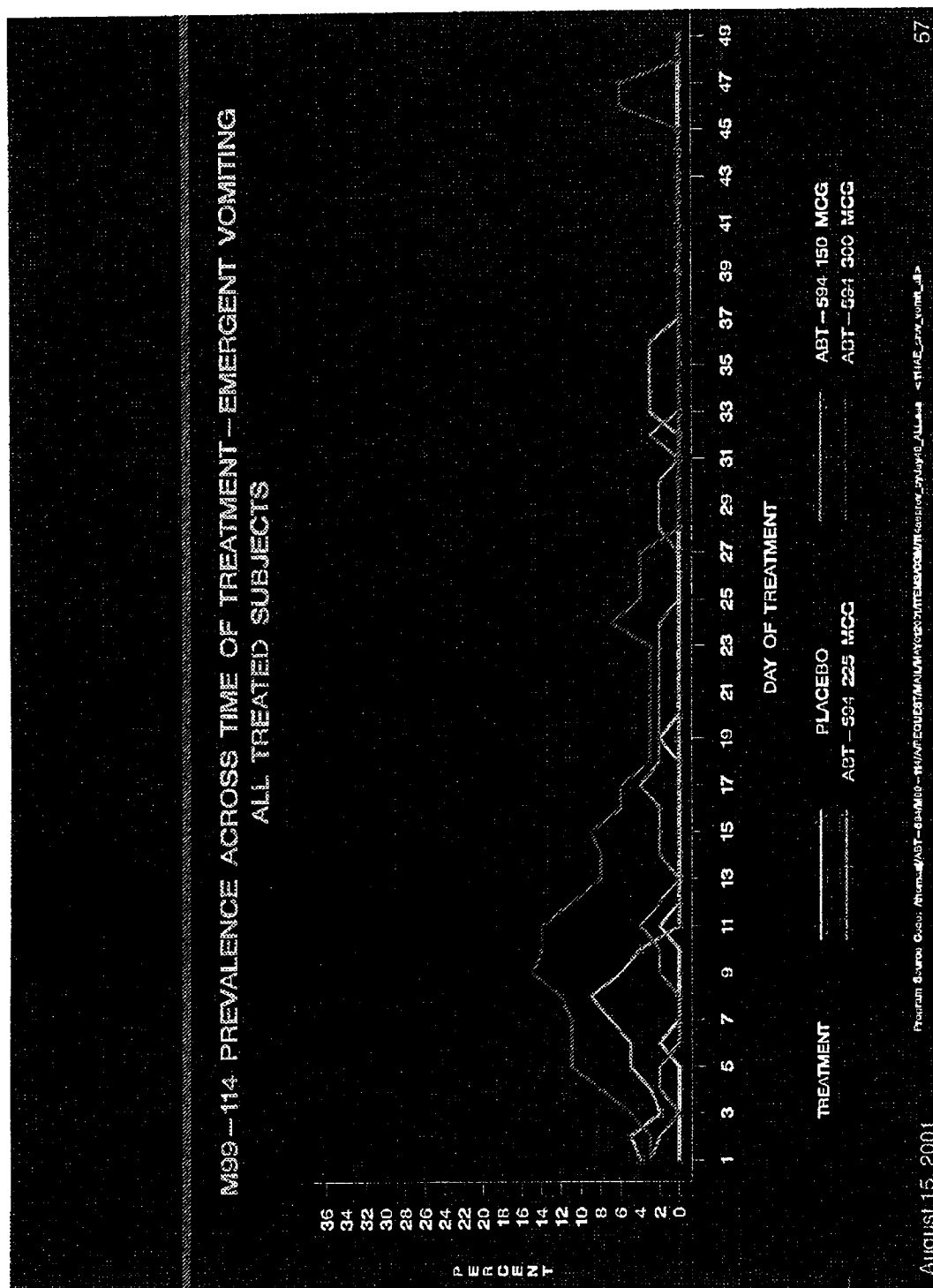


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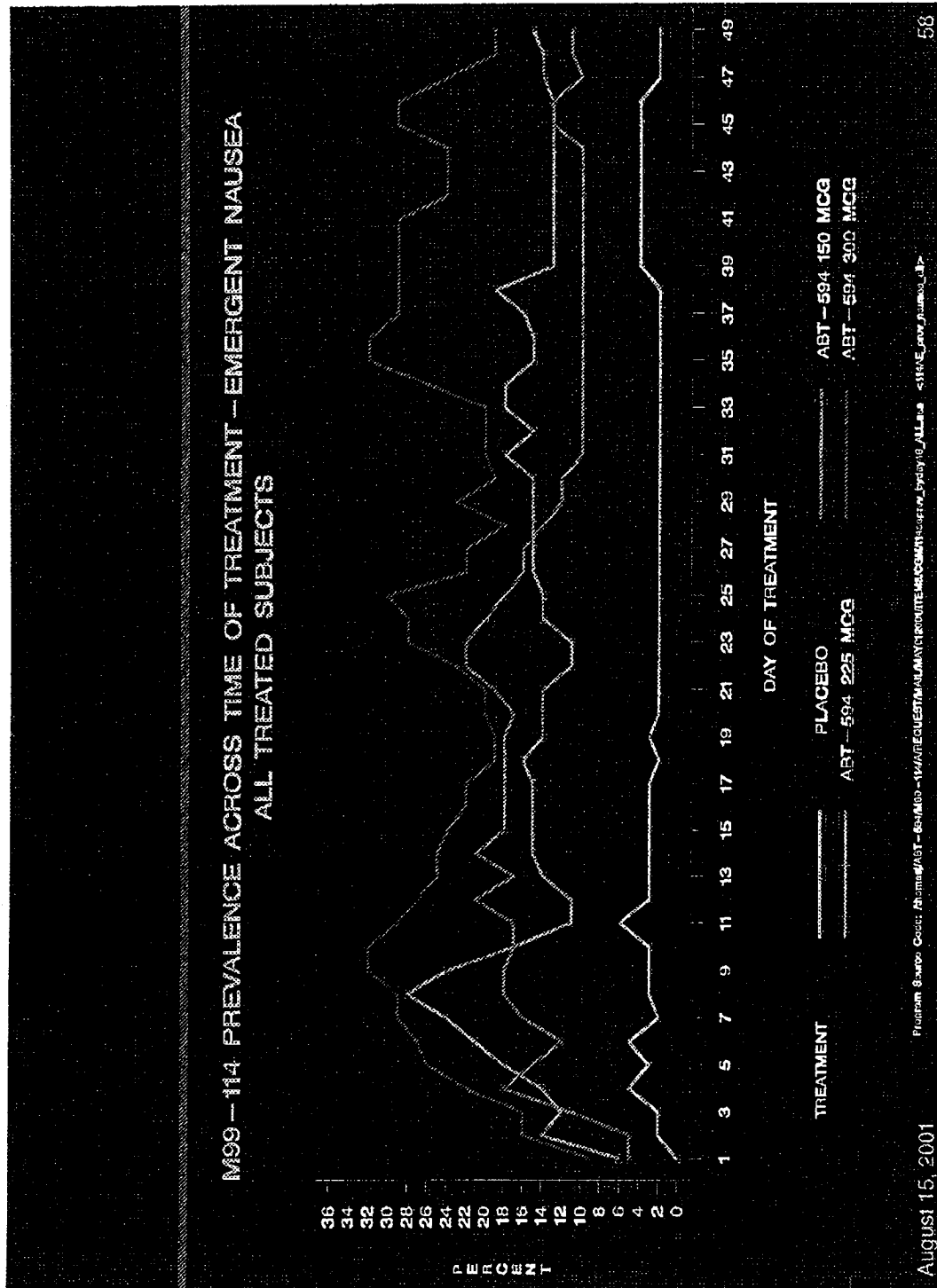
ABB T311574

56



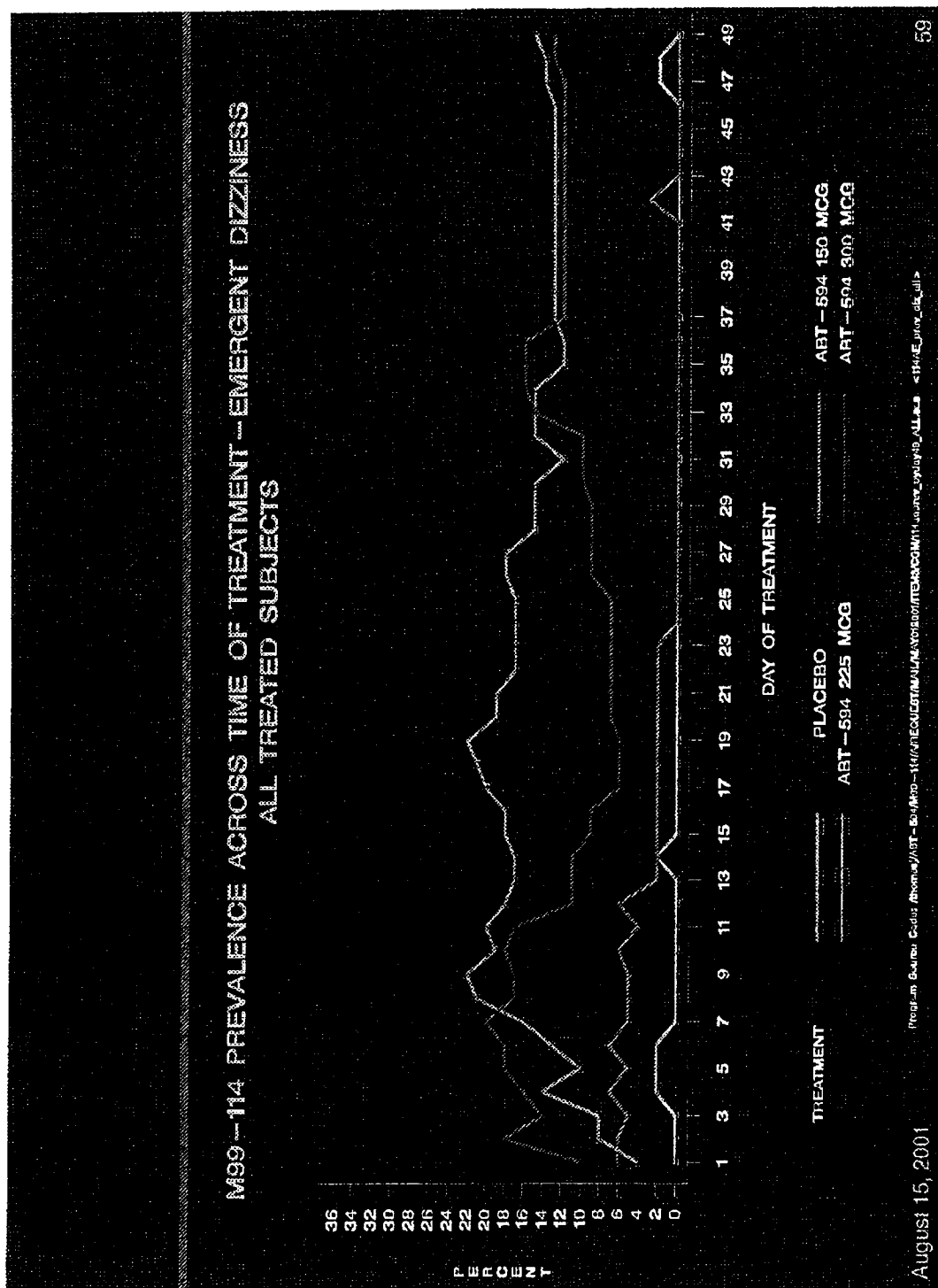
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ABB T311575



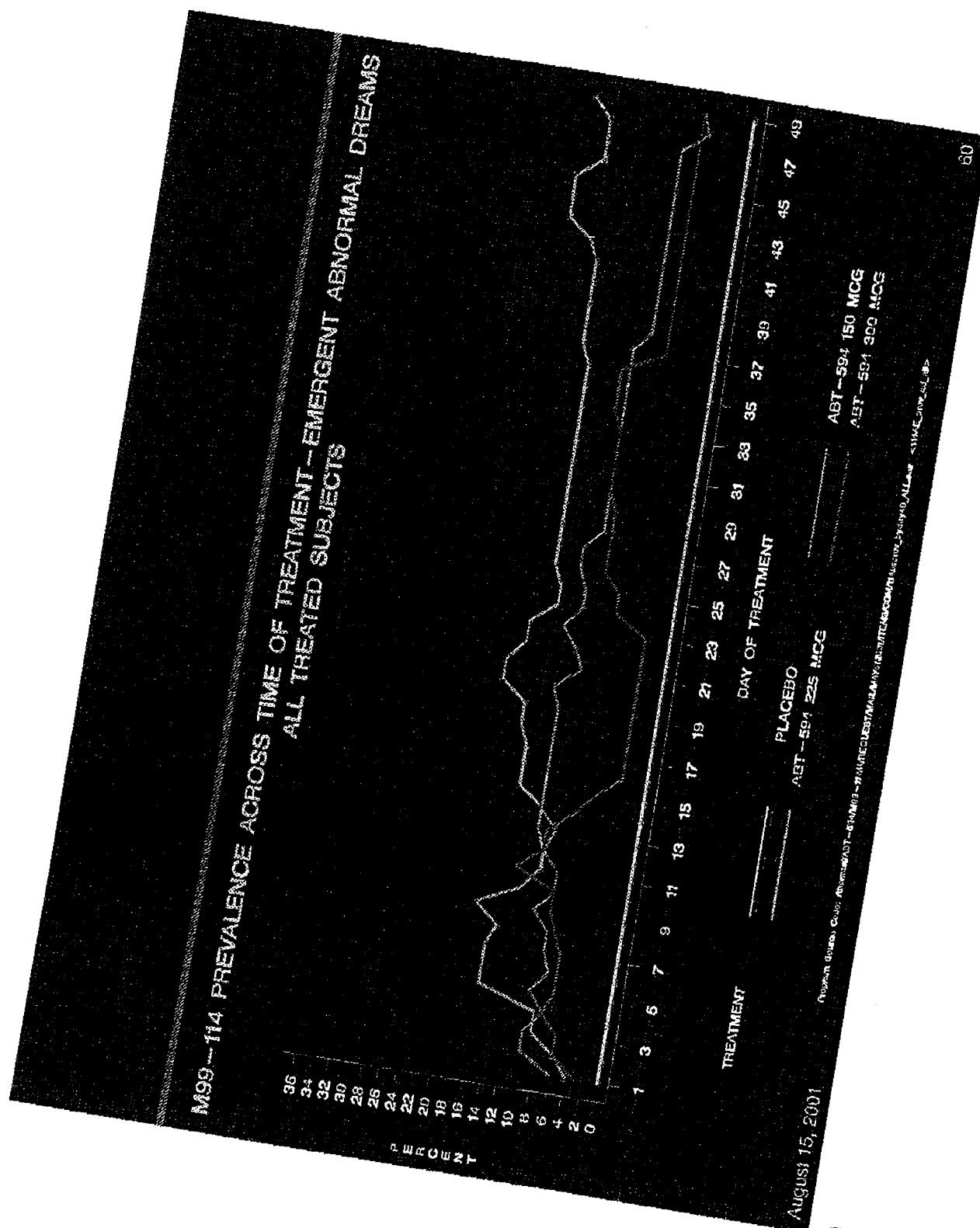
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ABBT311576



Confidential

ABBT311577



ABBT311578

Confidential

Completers vs. Preterms: initial analysis

- Significant Differences
 - Gender
 - Males were more likely to complete at 150 mcg (80% vs. 20% for males, 42% vs. 58% for females)
 - More females than males preterm due to adverse events (55% vs. 39%) when all ABT-594 groups were combined
 - Baseline Pain
 - Preterms had lower baseline pain than completers at 225 mcg BID (6.3 vs. 7.3, PRS diary)
 - Weight & Height
 - Preterms had lower weight & height than completers when ABT-594 groups were combined (196 vs. 207 lbs)
 - Nicotine Use
 - Fewer users and ex-users prematurely terminated than never users when all ABT-594 groups were combined (39% vs. 53%)
- No differences
 - Gender (225, 300)
 - Race
 - Age
 - Baseline Pain (150, 300)

61

August 15, 2001 — Baseline Pain (150, 300)

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ABBT311579

Completers vs. Preterms: Adverse Events

150 mcg BID

ABT-594

150 mcg BID

Completer
(N=40)

Preterm
(N=25)

Diarrhea	3 (8%)	4 (16%)
Nausea	10 (25%)	12 (48%)
Vomiting*	3 (8%)	7 (28%)
Abnormal Dreams	6 (15%)	8 (32%)
Dizziness*	3 (8%)	8 (32%)

Adverse events > 10%, more common in preterm

*p < 0.05

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62

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ABBT311580

Completers vs. Preterms: Adverse Events

225 mcg BID

ABT-594
225 mcg BID

	Completer (N=30)	Preterm (N=39)
Headache	3 (10%)	7 (18%)
Nausea	9 (30%)	21 (54%)
Vomiting*	3 (10%)	14 (36%)
Dizziness	9 (30%)	15 (38%)
Insomnia	2 (7%)	7 (18%)
Nervousness	0	4 (10%)

Adverse events > 10%, more common in preterm

*p < 0.05

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63

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ABBT311581

Completers vs. Preterms: Adverse Events

300 mcg BID

ABT-594

300 mcg BID

	Completer (N=17)	Preterm (N=50)
Asthenia	2 (12%)	11 (22%)
Vomiting	1 (6%)	13 (26%)
Abnormal Dreams	1 (6%)	11 (22%)
Insomnia	1 (6%)	6 (12%)
Nausea	8 (47%)	23 (46%)
Dizziness	6 (35%)	13 (26%)

Adverse events > 10%, more common in preterm

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64

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ABBT311582

Completers vs. Preterms: Adverse Events

All ABT-594 Subjects

	ABT-594 All Subjects	
	Completer (N=87)	Preterm (N=114)
Nausea*	27 (31%)	56 (49%)
Vomiting*	7 (8%)	34 (30%)
Abnormal Dreams	14 (16%)	27 (24%)
Dizziness	18 (21%)	36 (32%)
Insomnia	3 (3%)	14 (12%)

Adverse events > 10%, more common in preterm
* $p < 0.05$

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65

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ABBT311583

Premature Termination Benchmarks

- Gabapentin in Diabetic Neuropathy
 - GBP: 17% Total, 8% AE
 - PCB: 20% Total, 6 % AE
- Pregabalin in Diabetic Neuropathy
 - PGB:
- Tramadol in Diabetic Neuropathy

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66

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ABBT311584

Neuropathic Pain Reminder

Treatment Adverse Events Rates

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d
Confusion	N/A	N/A	8%	5%
Somnolence	66%	53%	23%	24%
Dizziness	28%	40%	24%	27%
Nausea	N/A	7%	8%	N/A
Peripheral edema	N/A	N/A	N/A	7%
Dry mouth	90%	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A

Confusion

Somnolence

Dizziness

Nausea

Peripheral edema

Dry mouth

Instability

¹ Max, 1987 (n=29)
N/A - Not Available

August 15, 2001

67

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ABBT311585

ABT-594 150, 225 and 300 mcg BID Were Associated with a Dose Dependent Increase in Adverse Events, Especially Nausea, Vomiting and Dizziness: All Subjects

Adverse Events

Event	ABT-594 150 mcg BID		ABT-594 225 mcg BID		ABT-594 300 mcg BID	
	N = 65	N = 65	N = 69	N = 69	N = 67	N = 67
Nausea	11 %	34 %*	43 %*		46 %*	
Abnormal Dreams	0 %	22 %*	22 %*		18 %*	
Headache	12 %	20 %	14 %		19 %	
Dizziness	5 %	17 %*	35 %*		28 %*	
Vomiting	3 %	15 %*	25 %*		21 %*	
Diarrhea	3 %	11 %	12 %		6 %	
Dyspepsia	3 %	8 %	12 %		7 %	
Asthenia	2 %	6 %	16 %*		19 %*	

Occurring in ≥5% 150 mcg BID ABT-594 treated patients and ABT-594 incidence > placebo.

*p<0.05 vs. placebo

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ABBT311586

95% Confidence Intervals for Nausea, Vomiting and Dizziness

Adverse Events

	150 mcg BID	225 mcg BID	300 mcg BID
Nausea	34% [22, 45]	43% [32, 55]	46% [34, 58]
Vomiting	15% [7, 24]	25% [14, 35]	21% [11, 31]
Dizziness	17% [8, 26]	35% [24, 46]	30% [19, 41]

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69

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ABBT311587

Increasing Levels of Pain Reduction May Trend with Increasing Incidence of Adverse Events at 300 mcg BID

300 mcg BID (ITT) Pain Reduction Quartiles

	Least Pain Reduction n=12	Quartile n=10	Quartile n=16	Most Pain Reduction n=15
Nausea	42%	40%	50%	60%
Vomiting	17%	20%	25%	27%
Dizziness	42%	0%	38%	20%

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70

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ABBT311588

Sample Size Is Too Small to Make Conclusions About The Relationship Between Level of Pain Reduction and Treatment Emergent Adverse Events for Completers

300 mcg BID (Completers) Quartile Pain Reduction

	Least Pain Reduction n=2	Quartile n=1	Quartile n=6	Most Pain Reduction n=8
Nausea	0%	0%	50%	63%
Vomiting	0%	100%	0%	0%
Dizziness	0%	0%	50%	38%

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71

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ABBT311589

QT Assessment

- M99-114 not designed to assess QT
- Mean QT
- Individual QTc (Bazett) Changes (on drug)
 - #4081: From 441 ms to 520 ms
 - Abt (BGM) re-read *would* be from 521 to 439 ms
- Syncope
 - #4083: h/o afib, to ER for “syncope”, refuses to release medical records

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72

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ABBT311590

ABT-594

Questions

- Where do doses evaluated to date fit on the dose-response curve?
 - * PK/PD Effect
- Can tolerability be improved?
 - * Differentiation of patient populations
 - * Dosage administration
- If tolerability is improved, will there be even more efficacy?
- How much will patients benefit from ABT-594?
 - * If administered as in M99-114
 - * Given hypothetical improvements in tolerability & efficacy

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73

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ABBT311591

McCarthy Deposition Exhibit 54

D's Exhibit 661

Part 4

ABT-594 IS A MAJOR SCIENTIFIC ACHIEVEMENT

- *Independent of future business decisions regarding ABT-594...*

- ABT-594 is the first drug ever to be successfully discovered and developed with the intent purpose to treat neuropathic pain (and other pain disorders).
- NNRs are now fully validated as a viable mechanism to treat neuropathic pain
- For the first time in decades there is now an additional class of analgesic agents:

- **NNRs**
- OPIOIDS
- NSAIDs/COX-2s
- ACETAMINOPHEN
- TCAs/AEDs

August 15, 2001

74

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ABBT311592

ABT-594

Pharmacokinetics and Metabolism

- Half-life ($t_{1/2}$): about 8-12 hours
- Dose proportional kinetics
- AUC, C_{max} similar across formulations (solution, SEC, HGC)
- AUC, C_{max} similar with/without food
- T_{max} varies somewhat with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about 50% unchanged drug recovered in urine

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75

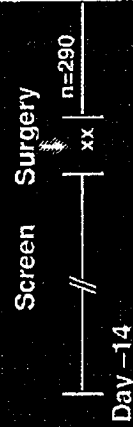
Confidential

ABBT311593

Molar Extraction Study

Design

- 290 patients, randomized, double-blind, placebo-controlled, single dose



n=50	ABT-594 100 mcg
n=46	ABT-594 75 mcg
n=50	ABT-594 50 mcg
n=46	ABT-594 25 mcg
n=48	Ibuprofen 400 mg
n=50	Placebo

- Third molar extraction
- Outcome measures:
 - Pain relief (PR)

Categorical scale:

0	1	2	3	4
none	a little	some	a lot	complete

- Power: 70% to detect an effect similar to acetaminophen plus codeine

- Solution

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76

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ABBT311594

Molar Extraction Study

Outcome Measures

- **Pain Relief (PR)**
 - Categorical scale: 0 none 1 a little 2 some 3 a lot 4 complete
- **Total Pain Associated Relief (TOTPAR)**
 - Area under the curve for PR (0-6 hours)
- **Pain Intensity (PI)**
 - Categorical scale: 0 none 1 mild 2 moderate 3 severe
 - Visual Analog Scale

no pain	worst pain
---------	------------
- **Stop Watch Model**
 - Time to “perceptible” and “meaningful” relief
- **Time To Rescue Medication**
- **Patient Global**
 - Rate medication: 1 poor 2 fair 3 good 4 excellent

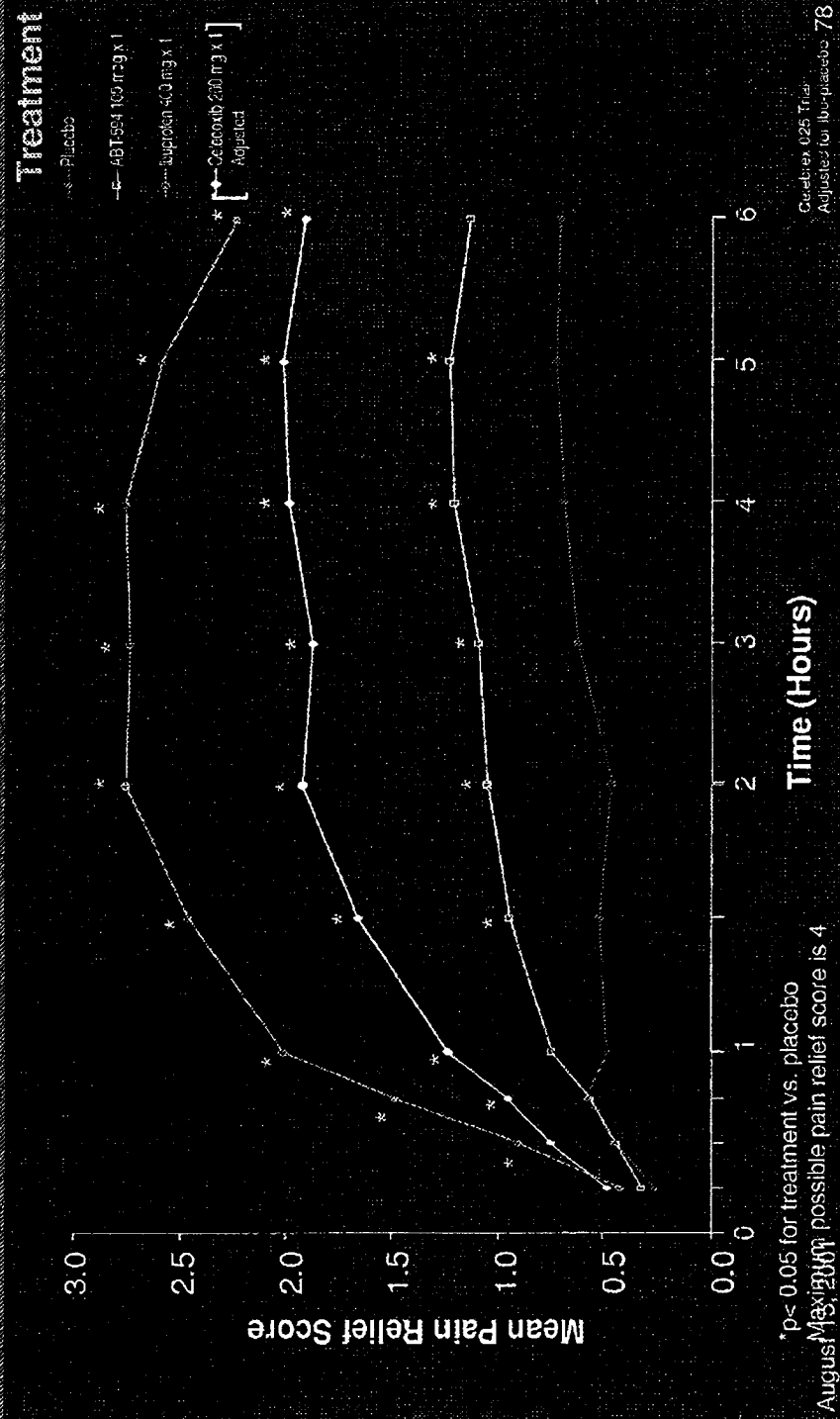
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77

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ABBT311595

ABT-594 100 mcg Is Significantly Better Than Placebo Starting 1.5 Hours After Dosing



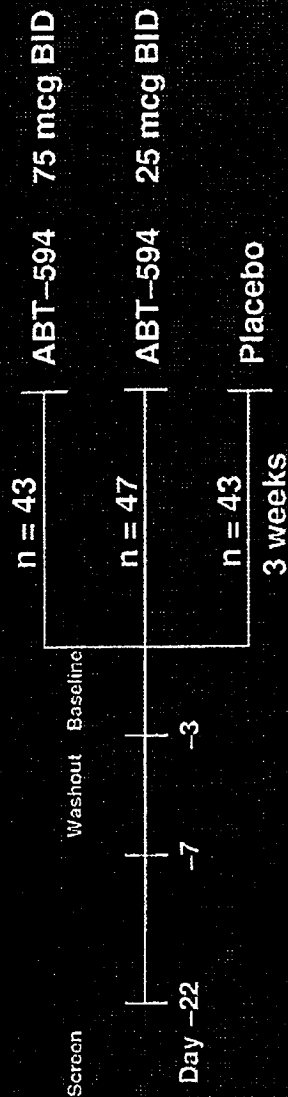
Confidential

ABBT311596

Neuropathic Pain Pilot

Design

- 133 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal symmetric polyneuropathy
 - 52% idiopathic
 - 46% diabetic
- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

August 15, 2001

79

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ABBT311597

Neuropathic Pain Pilot

Outcome Measures

• Pain Intensity (PI)

- Categorical Scale:
- | | | | |
|------|------|----------|--------|
| 0 | 1 | 2 | 3 |
| none | mild | moderate | severe |
-
- Visual Analog Scale:
(0-100 mm)
-

• Neuropathic Pain Scale (NPS)

- 10 items (e.g., sharp, hot, intense), for total 0-100 points
- Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts"

not sharp	1	2	3	4	5	6	7	8	9	10	The most sharp sensation imaginable ("like a knife")
-----------	---	---	---	---	---	---	---	---	---	----	--

• Patient Global (PG)

- Rate Medication:
- | | | | |
|------|------|------|-----------|
| 1 | 2 | 3 | 4 |
| poor | fair | good | excellent |

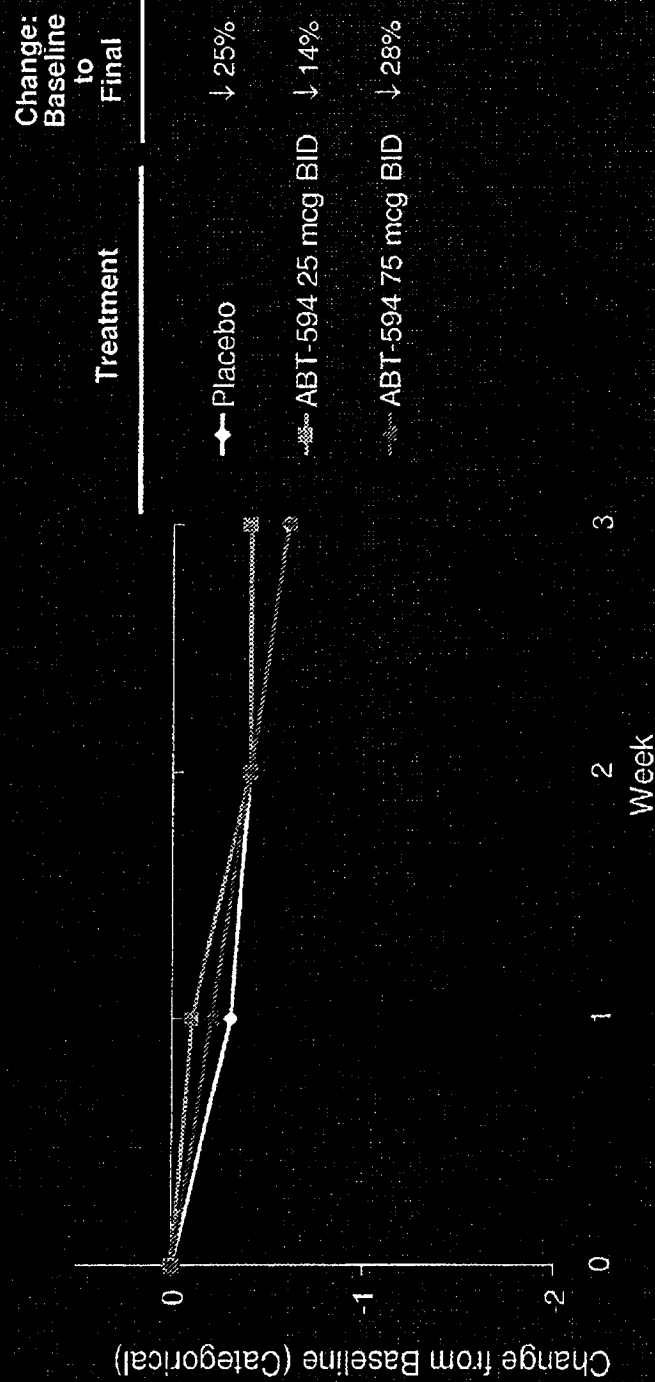
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80

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ABBT311598

ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared to Placebo in Neuropathic Pain



Maximum possible decrease for 75 mcg BID was 2.5

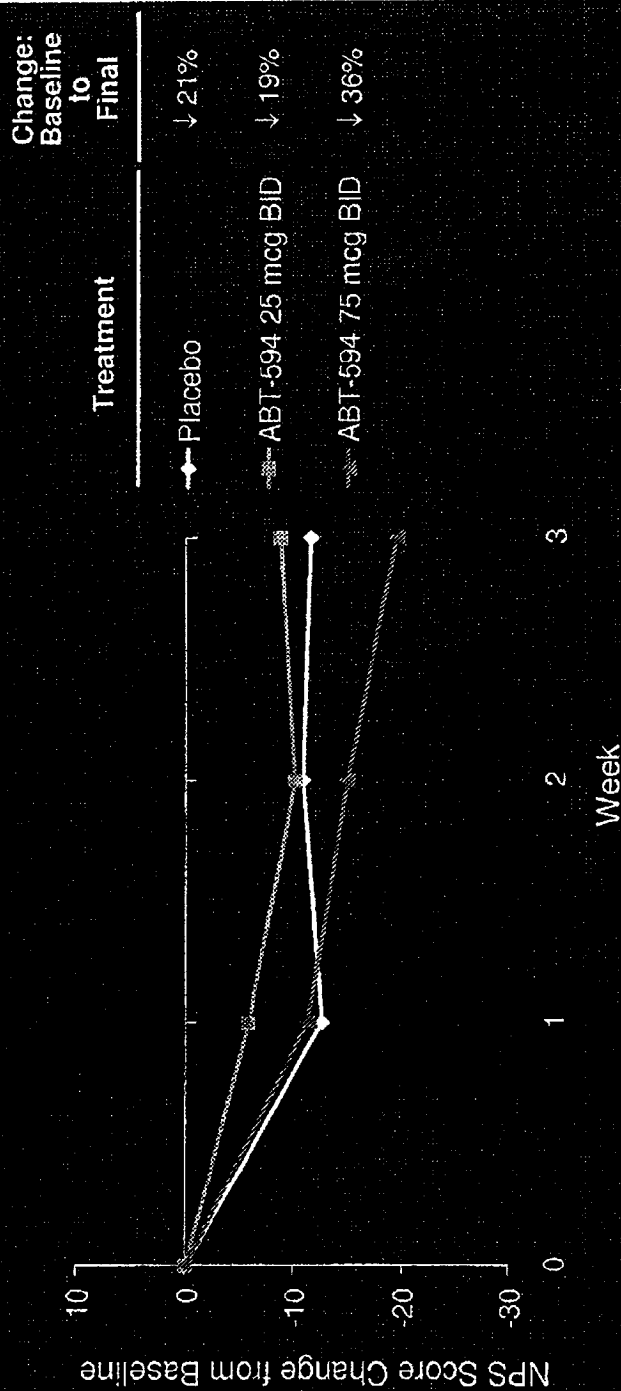
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Model-based ITT
LOCF
853 81

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ABBT311599

ABT-594 75 mcg BID Reduces the NPS More Than Placebo



Maximum possible decrease for 75 mcg BID was 59

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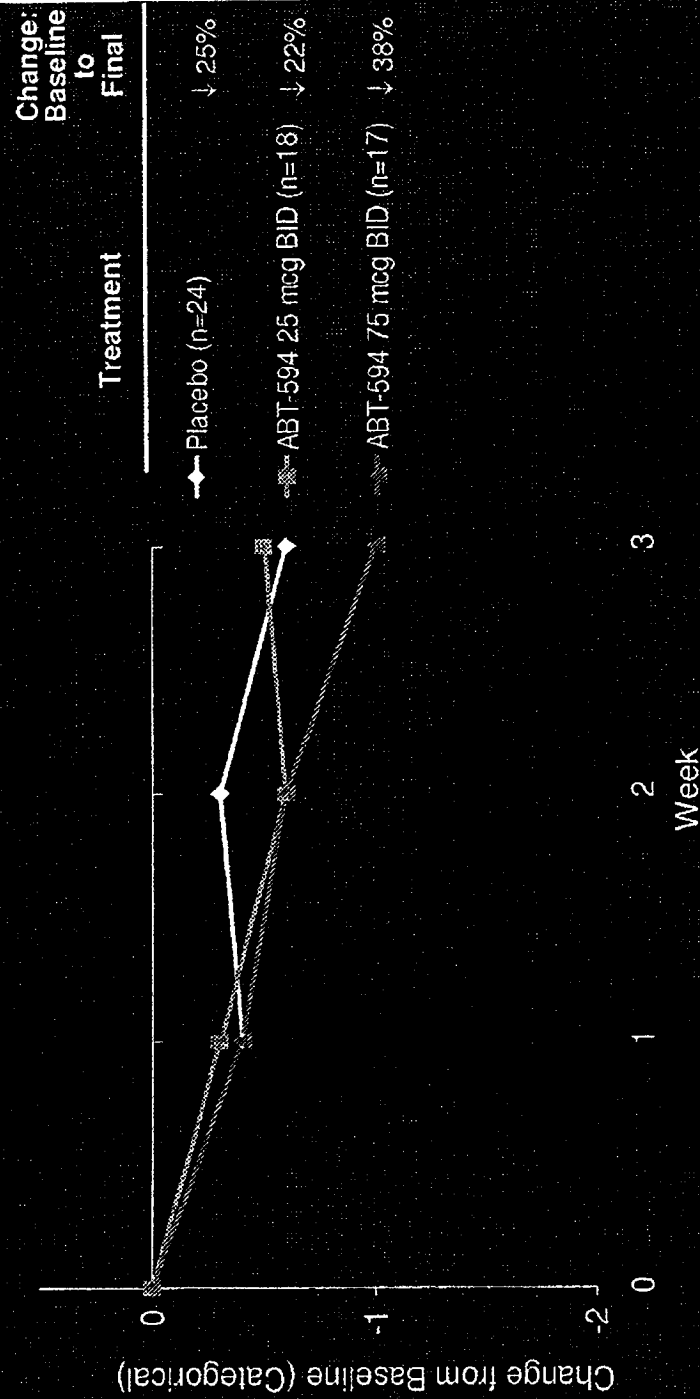
Model Based, IT
LOOF
833

82

Confidential

ABBT311600

ABT-594 75 mcg BID Reduces Daily Pain Score More Than Placebo in Diabetic Polyneuropathy



Maximum possible decrease for 75 mcg BID was 2.6

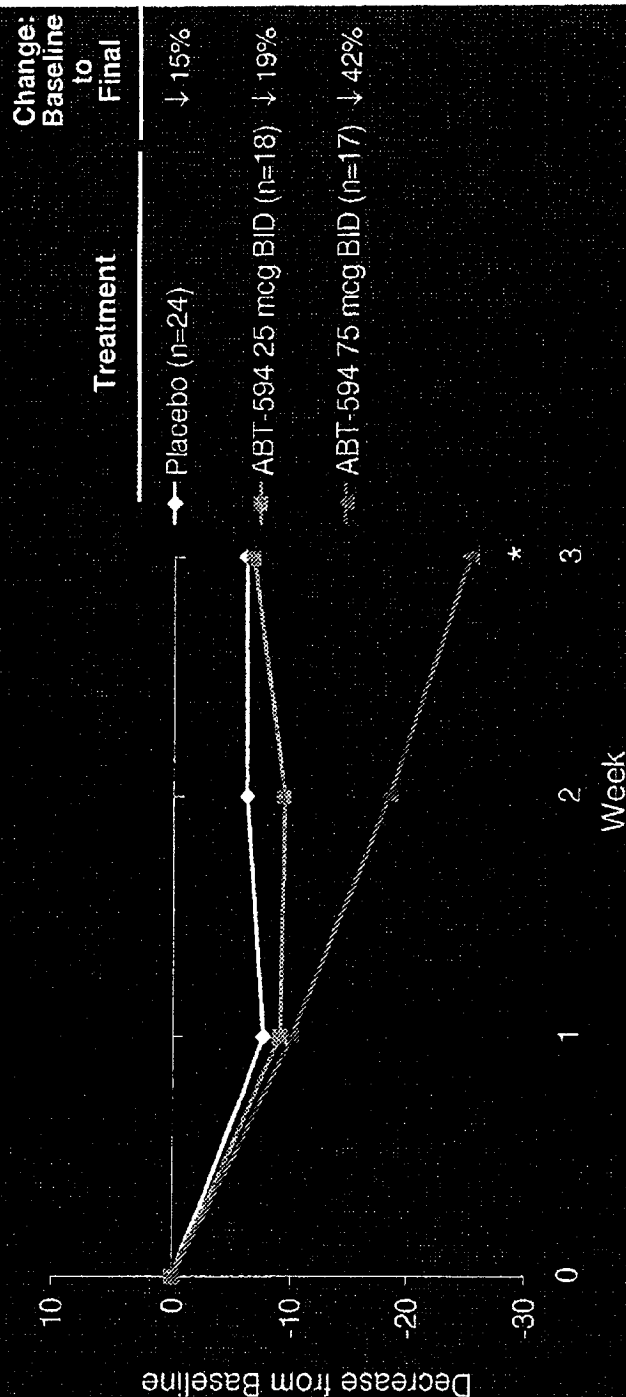
August 15, 2001

Medial based, ITT
LOCF
633 83

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ABBT311601

ABT-594 75 mcg BID Significantly Reduces NPS Compared to Placebo in Diabetic Polyneuropathy



* $p \leq 0.05$ vs. placebo
 Maximum possible decrease for 75 mcg BID was 52
 August 15, 2001

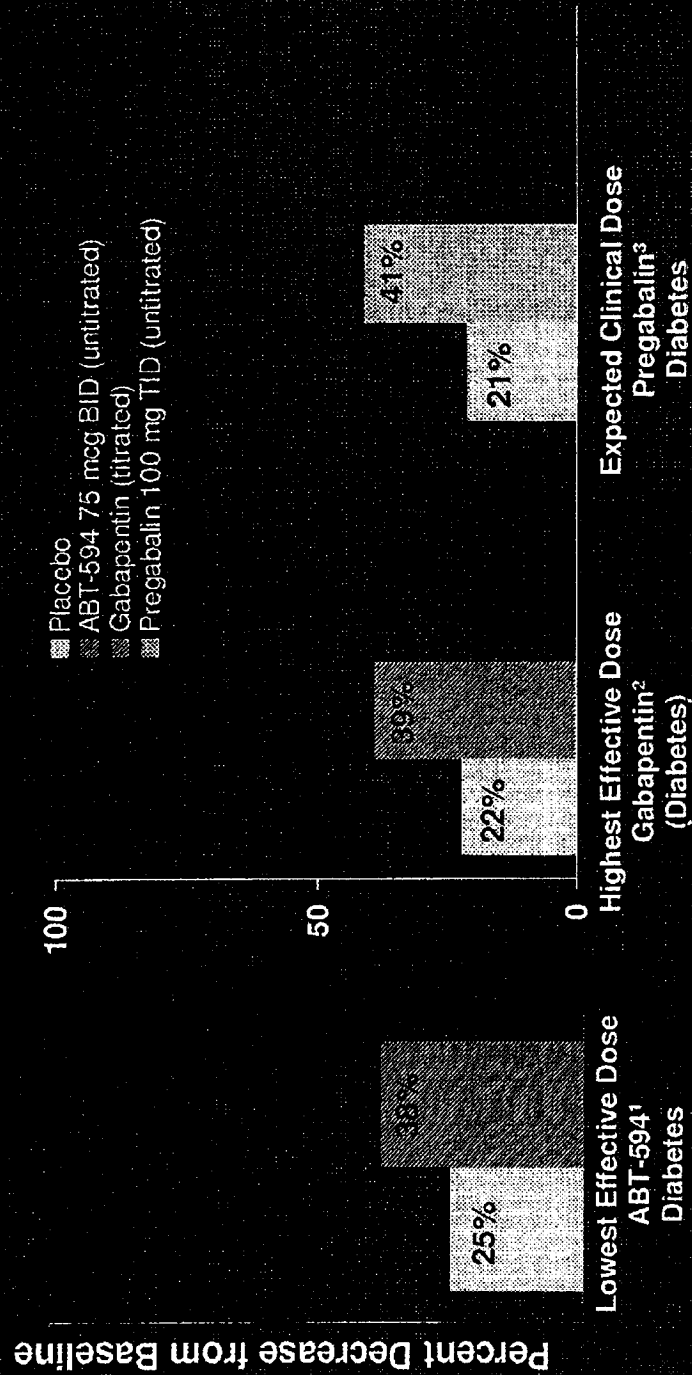
Model Based ITT
 LOCF
 84

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ABBT311602

ABT-594 75 mcg BID has a Similar Effect To Gabapentin

ABT-594 vs. Gabapentin and Pregabalin



¹ 4-point categorical scale final vs. baseline
² 11-point Likert Scale week 8 vs. baseline
³ 11-point Likert scale week 5 vs. baseline

August 15, 2001

85

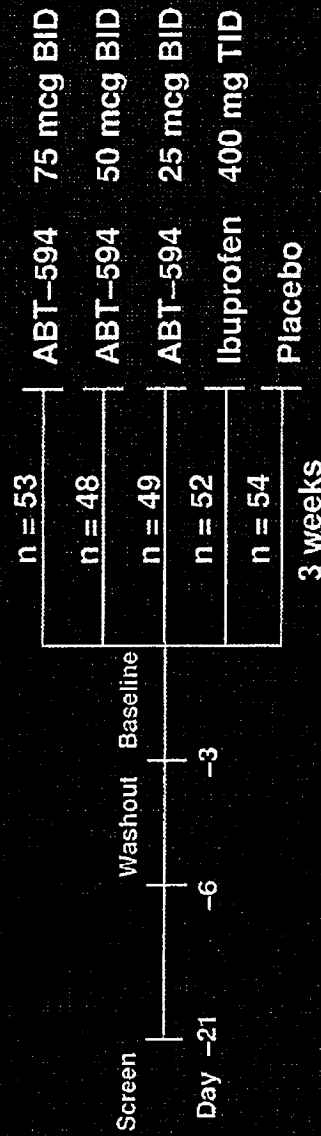
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ABBT311603

Osteoarthritis Pain Pilot

Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect a 20% difference (ABT-594 vs. placebo)
- Soft Elastic Capsule

August 15, 2001

86

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ABBT311604

Osteoarthritis Pain Pilot Study

Outcome Measures

- **Pain Intensity (PI)**

- Categorical Scale:

0	1	2	3
none	mild	moderate	severe

- Visual Analog Scale (VAS):



- **WOMAC**

- Pain (0-500)
 - Stiffness (0-200)
 - Function (0-1700)

Total (0-2400)

- **Patient Global**

- Rate Medication:

1	2	3	4
poor	fair	good	excellent

August 15, 2001

87

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ABBT311605

ABBT311606

Osteoarthritis Pain Pilot Study

WOMAC

Pain

How much pain do you have...

- Walking on a flat surface?
- Going up or down stairs

no pain | extreme pain

Stiffness

How severe is your stiffness...

- After sitting, lying, or resting later in the day?

no stiffness | extreme stiffness

Function

What degree of difficulty do you have...

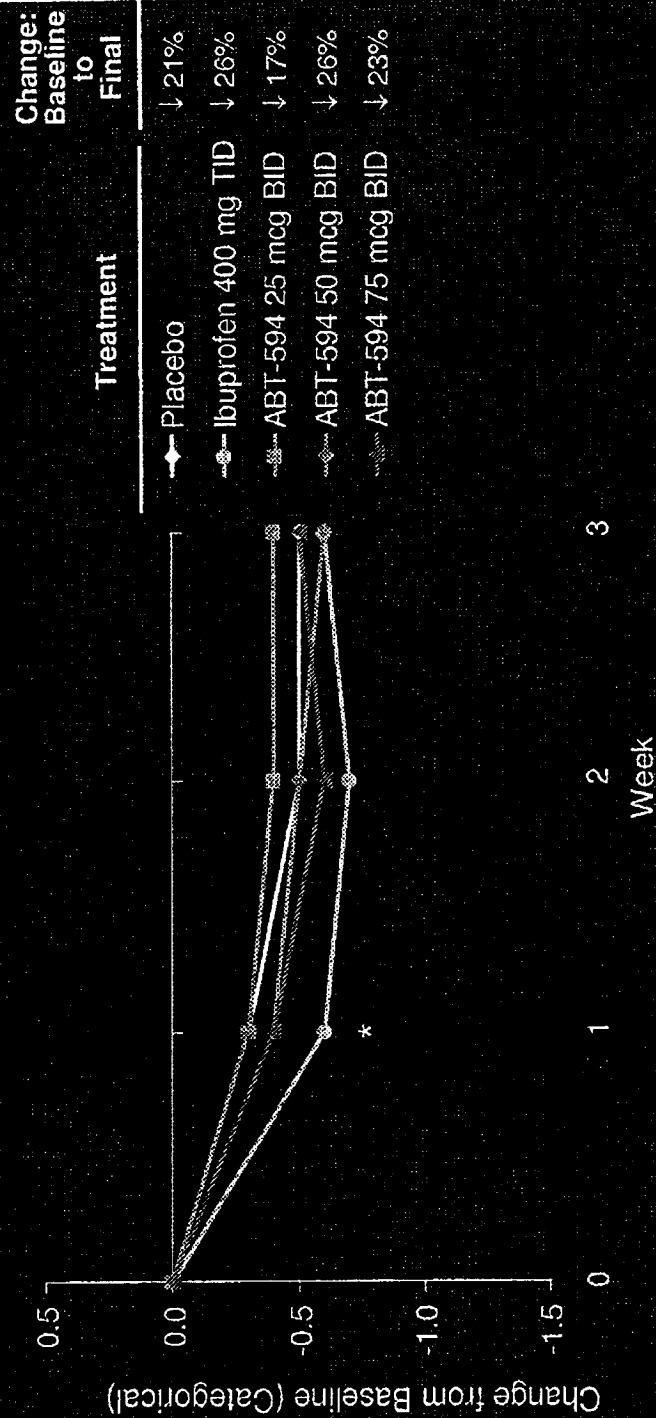
- Descending stairs?
- Rising from bed?

no difficulty | extreme difficulty

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ABT-594 75 mcg BID Does Not Reduce Daily Pain Score Compared To Placebo in Osteoarthritis



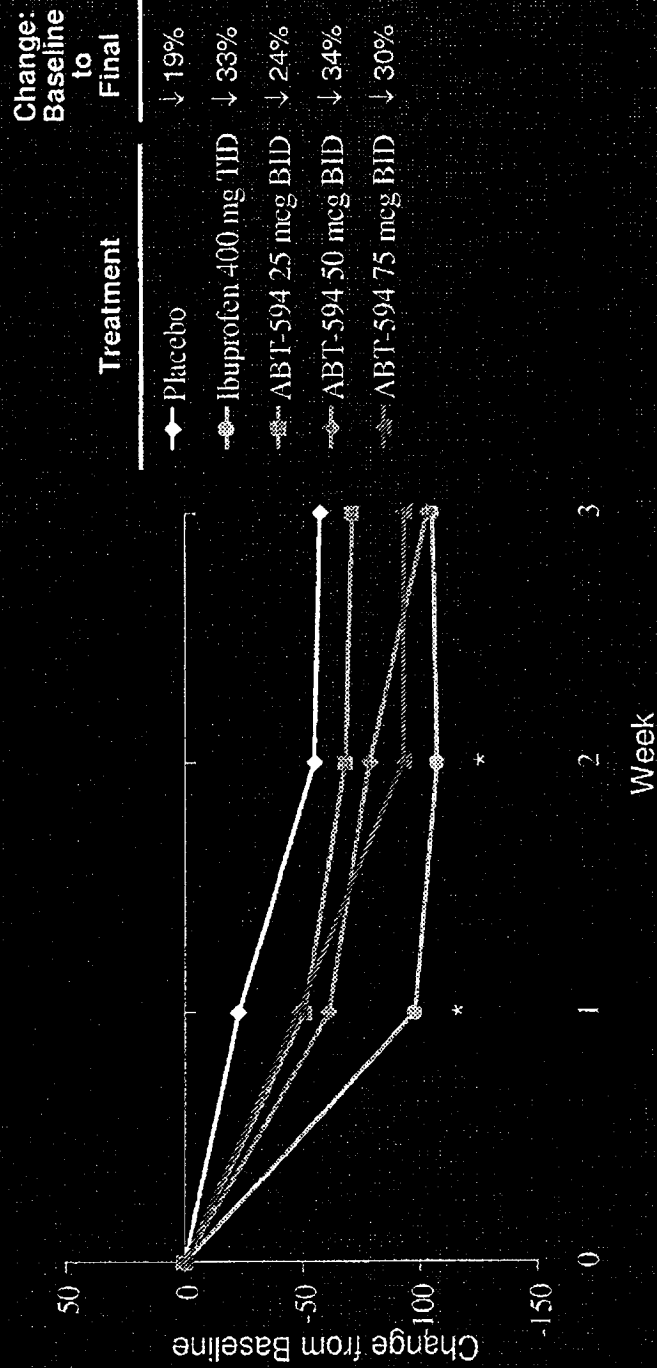
* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 2.2
August 15, 2001

Visual based, ITT
LOCF
89

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ABBT311607

ABT-594 75 mcg BID Reduces the WOMAC Pain Subscale More Than Placebo in Osteoarthritis



* $p \leq 0.05$ vs. placebo
Maximum possible decrease for 75 mcg BID was 305

Based on 5-item (0-500 points)

90

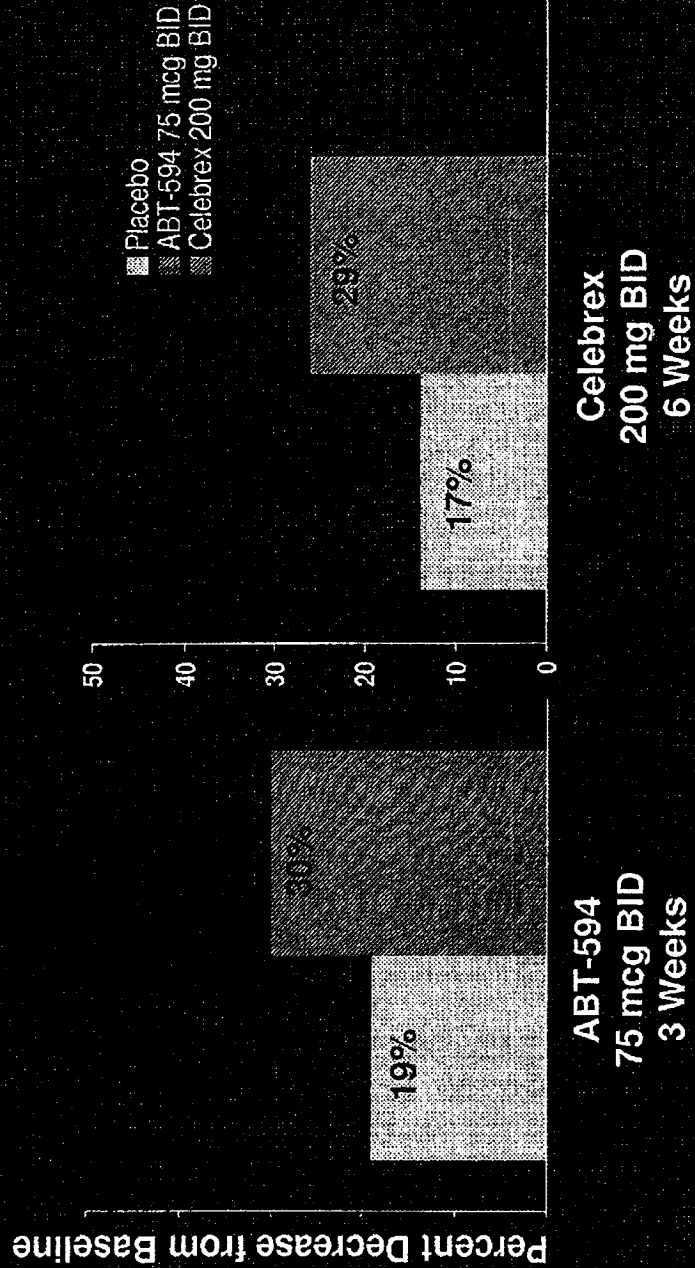
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ABBT311608

ABT-594 75 mcg BID Has An Effect Similar to Celebrex

WOMAC Pain Decrease from Baseline



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91

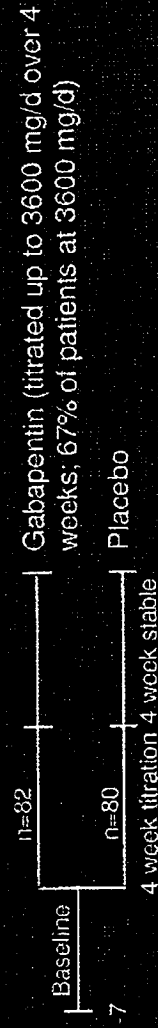
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ABBT311609

Gabapentin Study

Design

- 162 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- Power (planned): 75 patients/group, > 80% power to detect 25% difference (gabapentin vs. placebo)
- Entry: average ≥ 4 on 11-point Likert on at least 4 observations during baseline week; no concomitant analgesics

August 15, 2001

Backonja et al, 1998

Confidential

ABBT311610

Gabapentin Study

Outcome Measures

- Primary
 - 11-point Likert (0=no pain; 10=worst pain)
- Secondary
 - SFMPQ VAS no pain ————— worst possible pain
 - SFMPQ PPI
 - 0 no pain
 - 1 Mild
 - 2 Discomforting
 - 3 Distressing
 - 4 Horrible
 - 5 Excruciating
 - Patient global impression of change (7 point scale)

Backonja et al, 1998

August 15, 2001

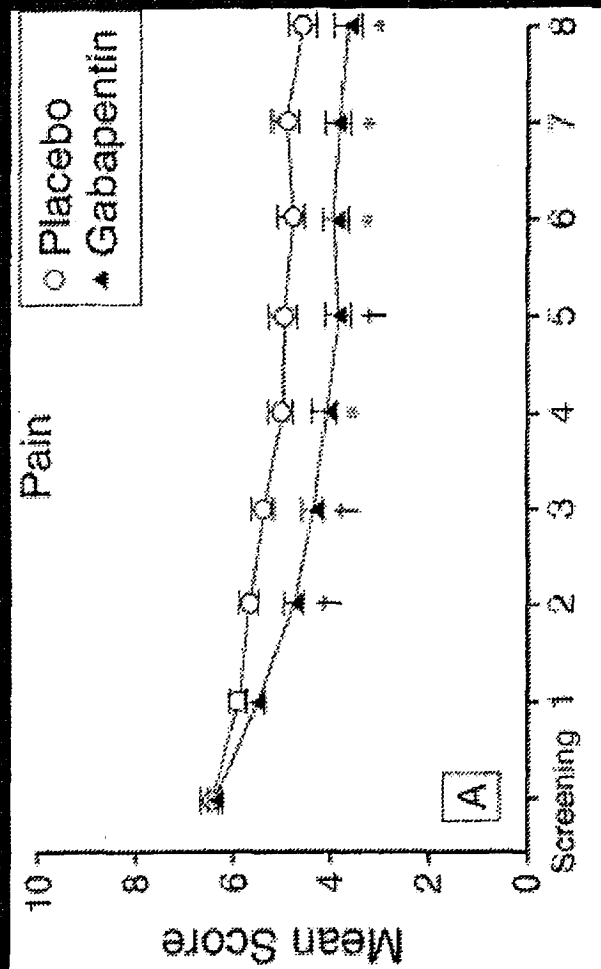
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ABBT311611

Gabapentin Study

Results

• Primary



Backonja et al, 1998

August 15, 2001

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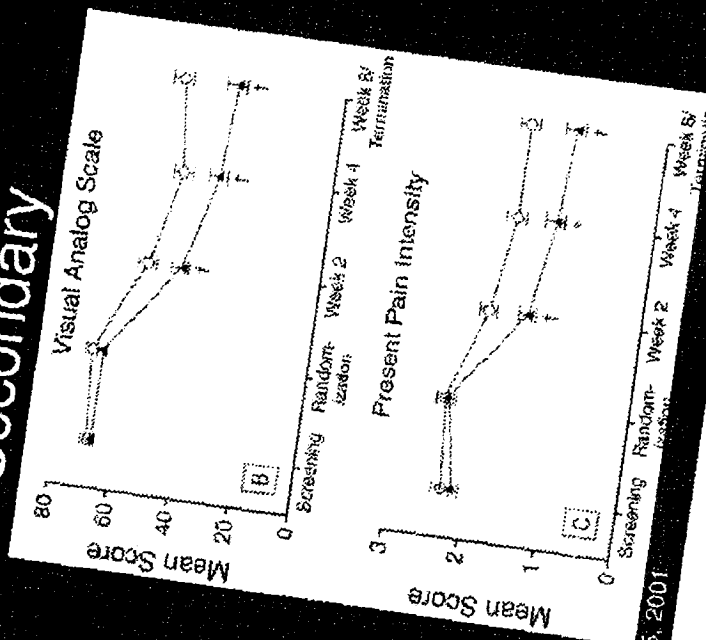
ABBT311612

ABB311613

Gabapentin Study

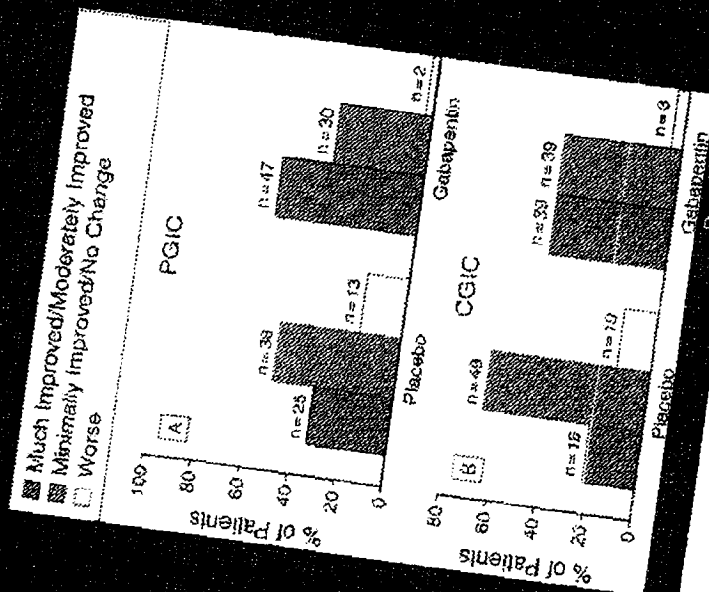
Results

Secondary



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Backopja et al. 1996

Gabapentin Studies

Adverse Events

	<u>Adverse Event Rate (%)</u>	
	Gabapentin	(placebo)
Dizziness	20	(4)
Somnolence	19	(5)
Headache	9	(3)
Diarrhea	9	(7)
Confusion	7	(1)
Nausea	7	(4)

Backonja et al, 1998

August 15, 2001

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ABBT311614

Pregabalin Studies

Design - 014

- 246 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
 - Average ≥ 4 on 11-point daily Likert during baseline
- Discontinuation due to adverse events:

600 mg/d	8.5%
150 mg/d	2.5%
Placebo	4.7%

Sharma et al, 2009

August 15, 2001

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ABBT311615

Pregabalin Studies

Outcome Measures - 014

- Primary
 - Weekly mean Likert pain score (probably)
- Secondary
 - Responder rate
 - Patient global impression of change
 - Sleep interference score
 - SFMPQ

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Sharma et al, 2008

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ABBT311616

McCarthy Deposition Exhibit 54

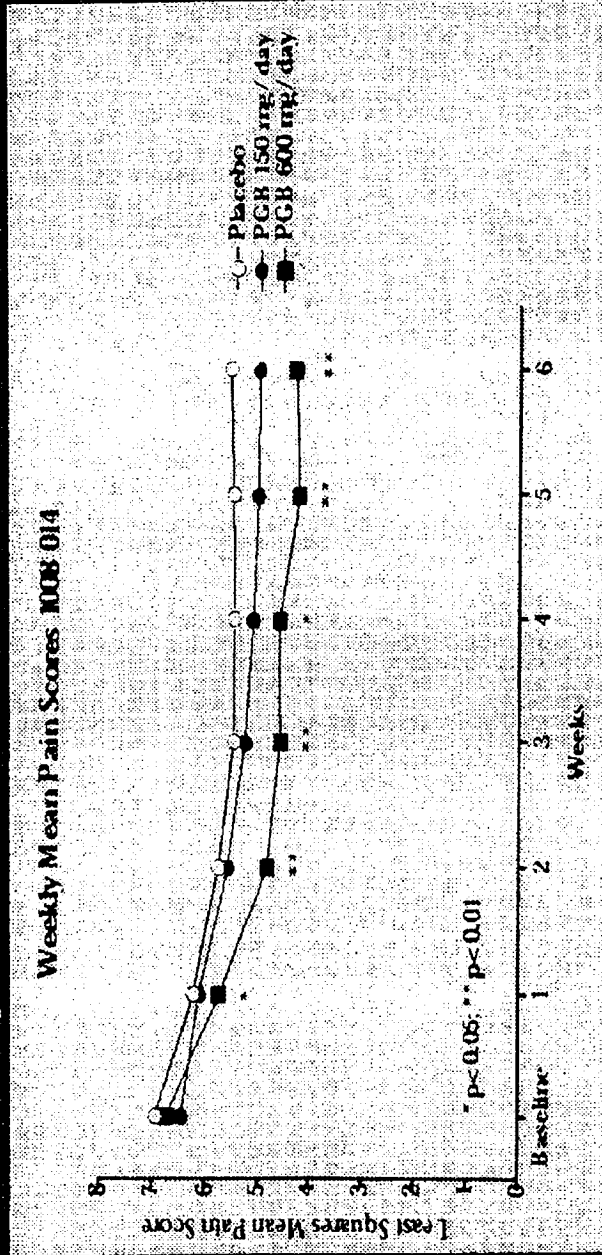
D's Exhibit 661

Part 5

Pregabalin Studies

Results - 014

Primary



Sharma et al, 2000

August 15, 2001

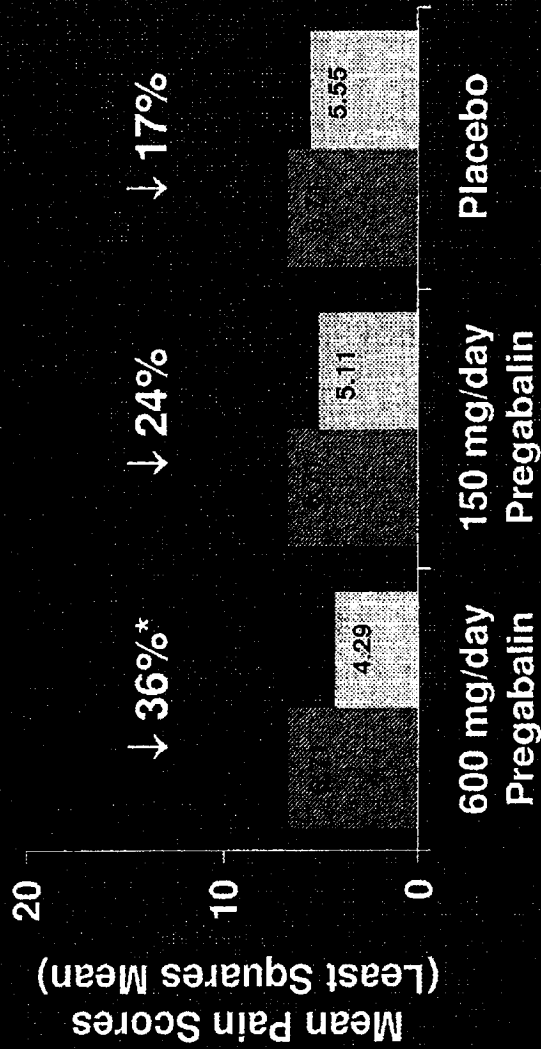
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ABBT311617

Pregabalin Studies

Results - 014

■ Baseline
■ Endpoint



*p=0.0002 vs. placebo
All data estimated from graph

Sharma et al, 2000

August 15, 2001

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ABBT311618

Pregabalin Studies

Responder Rate - 014

Responder Rate

600 mg/day	39%*
150 mg/day	15%
Placebo	12%

Responder = at least 50% reduction in
mean baseline pain score

*p=0.0002 vs. placebo

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Sharma et al, 2000

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ABBT311619

Pregabalin Studies

Adverse Events - 014

	600 mg/d (%)	150 mg/d (%)	Placebo (%)
Dizziness	37.8	10.1	2.4
Somnolence	22.0	5.1	3.5
Peripheral edema	17.1	3.8	4.7
Asthenia	12.2	3.8	3.5
Weight gain	9.8	2.5	0.0
Amblyopia	8.5	2.5	5.9
Dry mouth	8.5	0.0	2.4

Headache and accidental injury not included

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Sharma et al, 2000
102

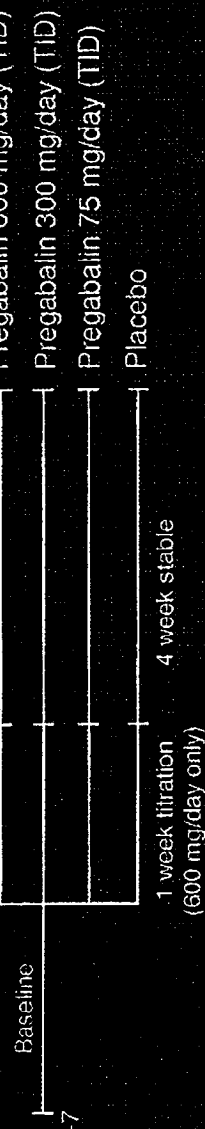
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ABBT311620

Pregabalin Studies

Design - 029

- 338 patients, randomized, double-blind, placebo-controlled



- Power not specified
- Entry
 - Average ≥ 4 on 11-point daily Likert during baseline
- Discontinuation due to adverse events:

600 mg/d	12.2%
300 mg/d	3.7%
75 mg/d	2.6%
Placebo	3.1%

Sharma et al, 2003

August 15, 2001

Confidential

ABBT311621

Pregabalin Studies

Outcome Measures - 029

- Primary
 - Weekly mean Likert pain score (probably)
- Secondary
 - Responder rate
 - Patient global impression of change
 - Sleep interference score
 - SFMPQ

Sharma et al, 2000

August 15, 2001

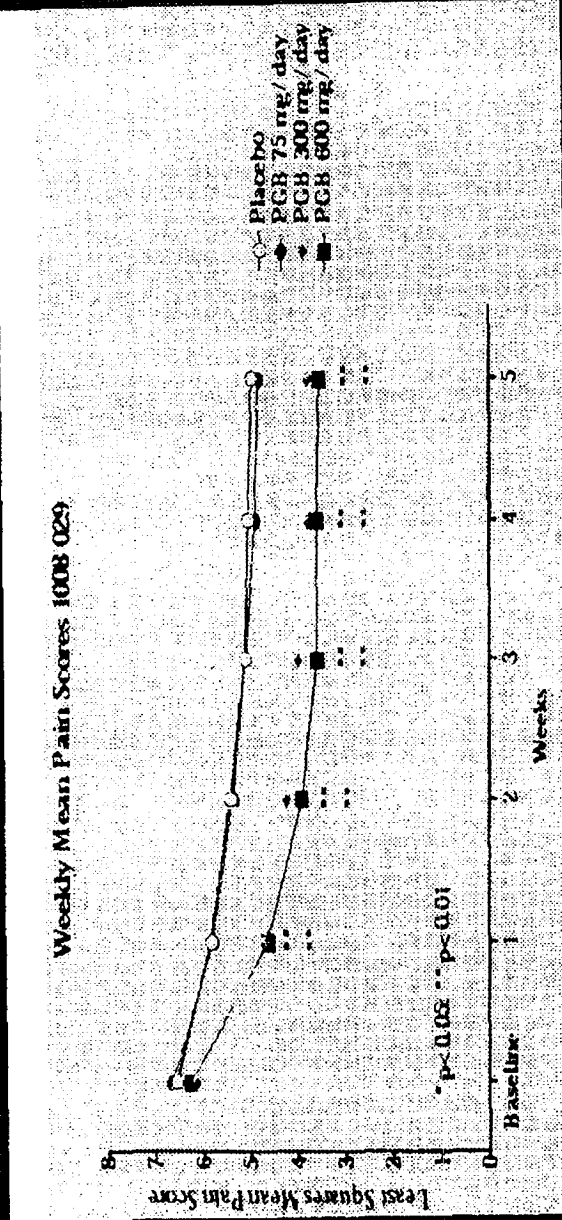
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ABBT311622

Pregabalin Studies

Results - 029

• Primary



Sharma et al, 2009

August 15, 2001

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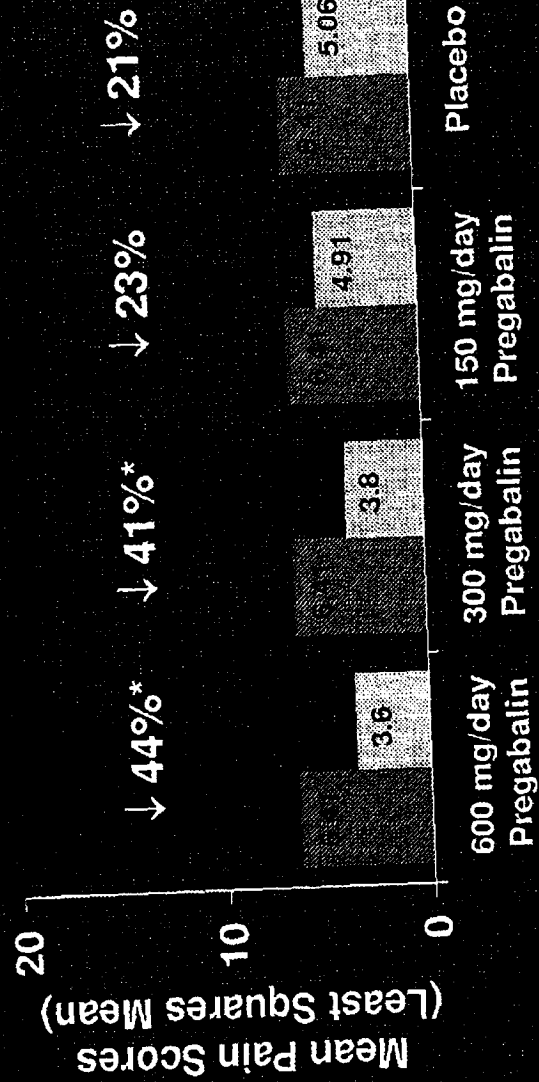
ABBT311623

ABBT311624

Pregabalin Studies

Results - 029

Baseline
Endpoint



*p=0.0001 vs. placebo

Sharma et al. 2000

August 15, 2001

Confidential

Pregabalin Studies

Responder Rate - 029

Responder Rate

600 mg/day	48.1%*
300 mg/day	45.7%*
75 mg/day	22.1%
Placebo	17.5%

Responder ≡ at least 50% reduction in mean baseline pain score

• $p=0.0002$ vs. placebo

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Sharma et al, 2009

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ABBT311625

Pregabalin Studies

Adverse Events - 029

	600 mg/d (%)	300 mg/d (%)	75 mg/d (%)	Placebo (%)
Dizziness	39.0	27.2	7.8	5.2
Somnolence	26.8	23.5	3.9	4.1
Peripheral edema	13.4	7.4	3.9	2.1
Amblyopia	8.5	4.9	2.6	1.0
Ataxia	8.5	3.7	6.5	2.1
Confusion	8.5	4.9	0.0	2.1
Constipation	8.5	3.7	0.0	0.0

Headache not included

Sharma et al, 2008

August 15, 2001

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ABBT311626

Pregabalin Studies

Responder Rate - 131

Responder Rate

300 mg/day

40.0 %*

Placebo

14.5 %

Responder \equiv at least 50% reduction in
mean baseline pain score

• $p=0.001$ vs. placebo

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Sharma et al, 2000

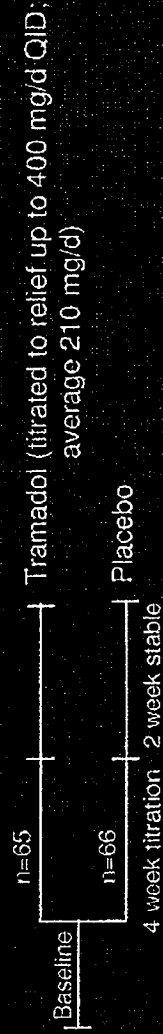
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ABBT311627

Tramadol Study

Design

- 131 patients, randomized, double-blind, placebo-controlled, multiple dose



- Diabetic polyneuropathy
- Power: 85% to detect a difference of 0.8 (on 5-point scale, tramadol vs. placebo)
- Moderate (2) or greater; no concomitant analgesics

Marati et al, 1998
118

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ABBT311628

Tramadol Study

Outcome Measures

• Primary

- 5 point Likert pain intensity (at visits)

0 none
1 mild
2 moderate
3 severe
4 extreme

• Secondary

- Patient rated pain relief score

Complete 4
A lot 3
Moderate 2
Slight 1
None 0
Worse (-1)

- Medical Outcome Study measures of daily living activities and sleep

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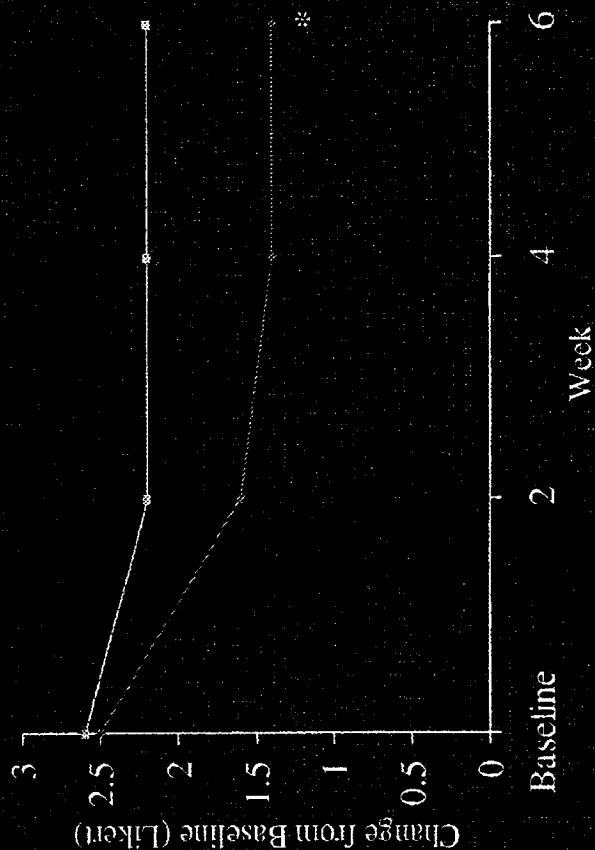
Marati et al. 1998

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ABBT311629

Tramadol Study

Results: Primary



* $p < 0.001$ vs. placebo
 Maximum possible decrease for tramadol was 2.5
 Some data estimated from graphical presentation

August 15, 2001

Treatment	Change: Baseline to Final
Tramadol	↓ 44%
Placebo	↓ 15%

Marati et al, 1998

Confidential

ABBT311630

Tramadol Study

Adverse Events

	<u>Adverse Event Rate (%)</u>	
	Tramadol	(placebo)
Nausea	23	(3)
Constipation	22	(3)
Somnolence	12	(6)
Dyspepsia	9	(3)
Pruritis	6	(0)
Rash	6	(0)
Vomiting	5	(0)
Fatigue	5	(0)
Dizziness	5	(0)

Marati et al, 1998

August 15, 2001

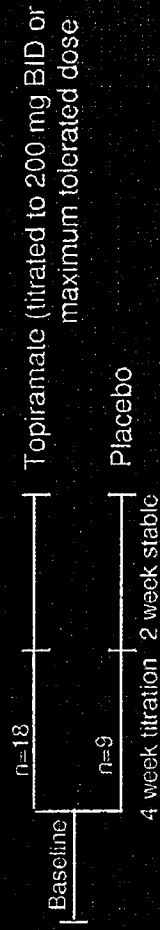
Confidential

ABBT311631

Topiramate Study

Design

- 27 patients, randomized (2:1 topiramate to placebo), double-blind, placebo-controlled



- Diabetic polyneuropathy
- Not powered
- Entry
 - No concomitant analgesic medications
 - ≥ 40 mm/100 mm SFMPQ-VAS at baseline visit
 - ≥ 4 on 11-point Likert pain scale at baseline visit

Edwards et al, 1999

August 15, 2001

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ABBT311632

Topiramate Study

Outcome Measures

- Primary
 - SFMPQ-VAS
- Secondary
 - SFMPQ-Total
 - Patient global impression of change

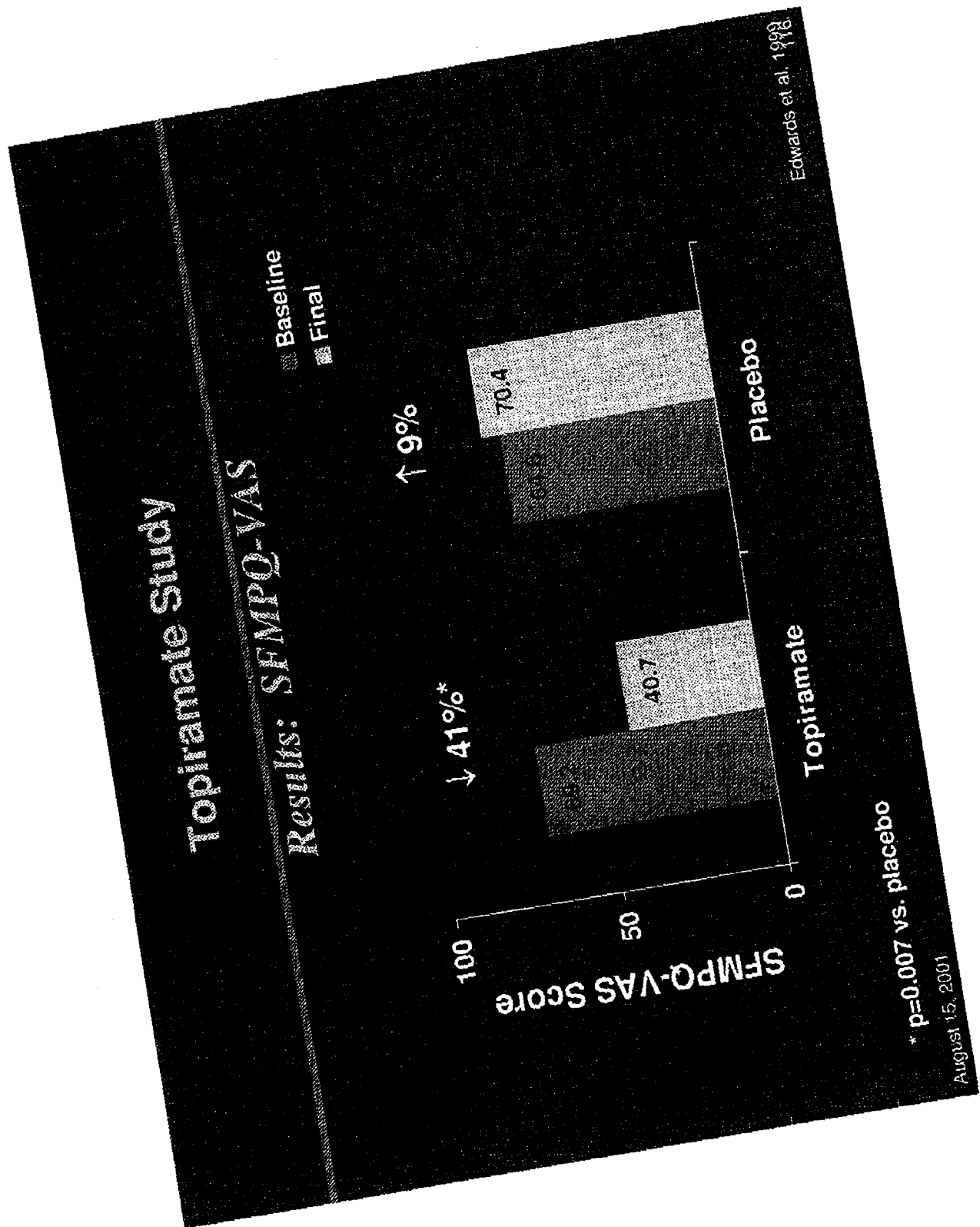
Edwards et al, 1999
115

August 15, 2001

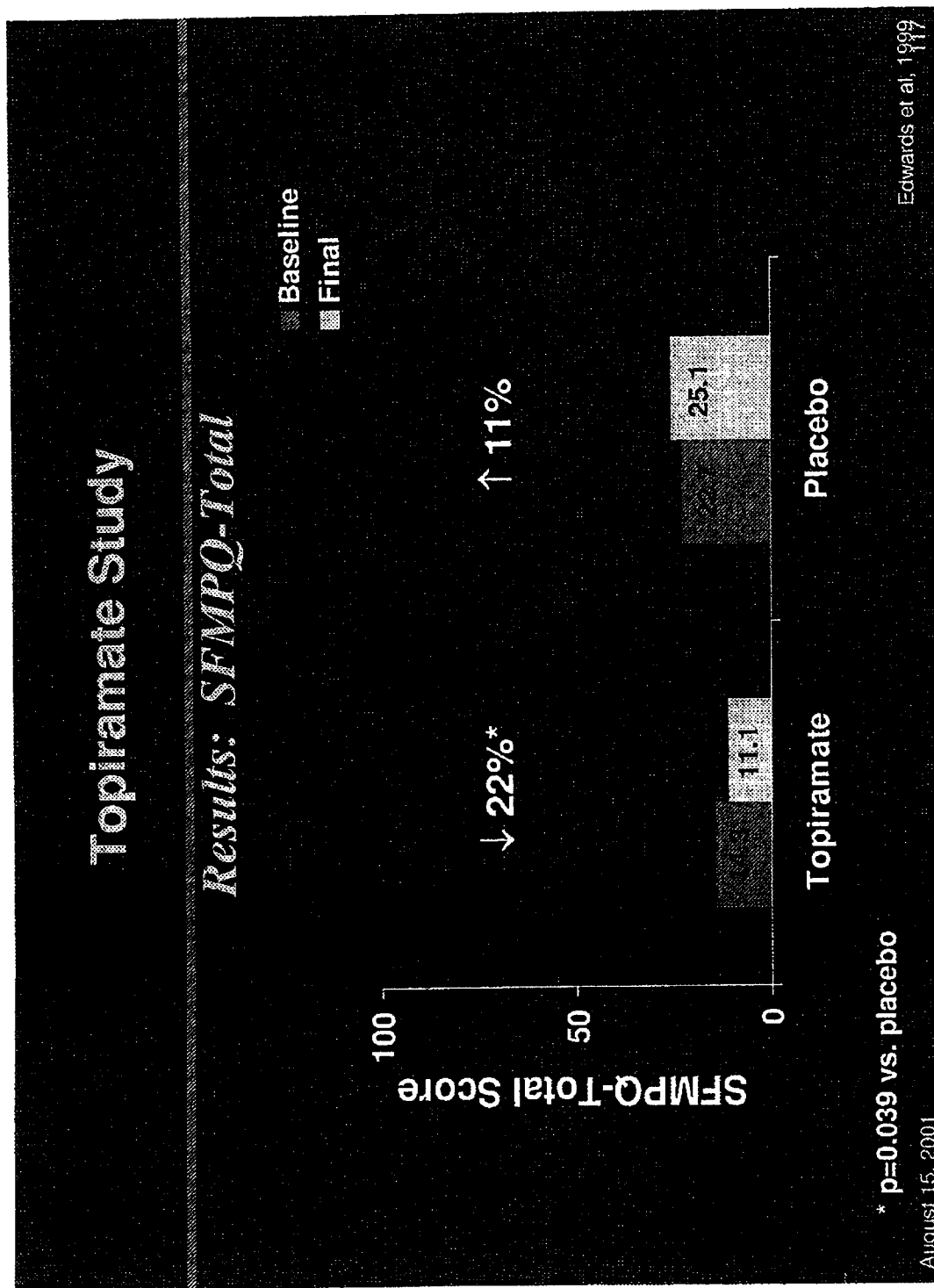
Confidential

ABBT311633

ABBT311634



Confidential



ABBT311635

Confidential

Topiramate Study

Adverse Events

Adverse Event Rate (%)

Topiramate (placebo)

Asthenia	56	(0)
Weight loss of > 10%	22	(0)
Confusion	22	(0)
Paresthesia	17	(0)
Lightheadedness	17	(0)
Dry mouth	17	(0)

Edwards et al, 1999

August 15, 2001

Confidential

ABBT311636

Amitriptyline for Neuropathic Pain

Max, 1987

- Largest (active) placebo-controlled, randomized, double-blind trial of a tricyclic
 - N=29 (completers); 5 discontinued due to AEs
 - 2-week drug-free baseline, 6-week crossover (no washout): 3-week titration, 3-week stable (150 mg)
- Primary endpoint – 13 word verbal description (numeric equivalents)

Placebo	↓ 14%	
Amitriptyline	↓ 51%	(estimated from graph)
- Adverse events

Dry mouth	90%
Sedation	66%
Dizziness	28%
Constipation	14%

August 15, 2001

119

Confidential

ABBT311637

McCarthy Deposition Exhibit 59

P's Exhibit HO



Bruce
McCarthy/LAKE/PPR
D/ABBOTT
10/10/2001 12:34 PM

To: Michael K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT
Philip M Deemer/LAKE/CORP/ABBOTT@ABBOTT, Danhui
cc: Wang/LAKE/PPD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject: Re: ABT-594 Update

Mike-

We will need to have a discussion off-line from the main project meeting (doesn't need to be before) at which we can begin discussions of how we handle ABT-594 as an asset. Out-licensing 594 may have negative impact upon the value of the follow-ons, independent of the likelihood of success of out-licensing. The meeting should include you and me, Danhui, Phil and Jim.

Bruce.
Danhui Wang



Danhui Wang
10/10/2001 11:48 AM

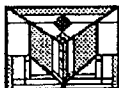
To: Michael K Biarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Philip M
Deemer/LAKE/CORP/ABBOTT@ABBOTT
cc: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Catherine K
Kacos/LAKE/PPRD/ABBOTT@ABBOTT, Elizabeth
Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT, Damien
Springuel/LAKE/AV/ABBOTT@ABBOTT, Kevin P
Constable/LAKE/PPRD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Chrys
Kokina/LAKE/PPD/ABBOTT@ABBOTT, Paul L
Berns/LAKE/PPD/ABBOTT@ABBOTT, Andres
White/LAKE/AV/ABBOTT@ABBOTT

Subject: Re: ABT-594 Update

Thank you very much, Mike. I really appreciate the update.
I will talk to Phil concerning the potential for out-licensing
ABT-594. Meanwhile, the whole team (Discovery, Venture,
GNPP, Franchise, and Business Development) needs to think through
as to what options in out-licensing we have and which option we
choose to pursue.

Danhui Wang
Sr. Manager, Global New Product Planning
Abbott Laboratories
Tel: (847) 935-0994
Fax: (847) 935-3128
email: danhui.wang@abbott.com

Michael K Biarnesen

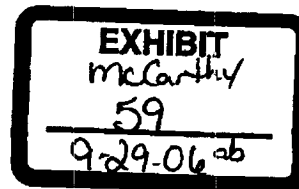


Michael K Biarnesen
10/10/2001 09:05 AM

To: Danhui Wang/LAKE/PPD/ABBOTT@ABBOTT, Philip M
Deemer/LAKE/CORP/ABBOTT@ABBOTT, Elizabeth
Kowaluk/LAKE/PPRD/ABBOTT@ABBOTT
cc: Catherine K Kacos/LAKE/PPRD/ABBOTT@ABBOTT, Bruce

Confidential

ABBT245657





McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT-594 Project Team Update

Danhui, Phil and Liz,

Can you let me know if there is any potential of outlicensing this product? If there is, then our wrapup activities need to be different than if we are strictly shelving the program for good

Cathy - Please send Danhui, Phil and Liz an invite to the meeting

Thanks,

Mike Blarnesen
Operations Manager, Neuroscience Venture
Abbott Laboratories Global Pharmaceutical R&D
(847)938-6514 Fax: (847)938-5258

----- Forwarded by Michael K Blarnesen/LAKE/PPRD/ABBOTT on 10/10/01 09:02 AM -----



Catherine K Kacos
10/10/01 08:26 AM

To: Laura Robinson/LAKE/HPD/ABBOTT@ABBOTT, Marilyn J
Collicott/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T
Matalonis/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT, Carol J
Feigel/LAKE/PPRD/ABBOTT@ABBOTT, Marian L
Borgstrom/LAKE/PPRD/ABBOTT@ABBOTT, Raymond A
Morales/LAKE/PPRD/ABBOTT@ABBOTT, Joan M
Freehoff/LAKE/PPRD/ABBOTT@ABBOTT, Robert
O'Dea/LAKE/PPRD/ABBOTT@ABBOTT, Susan E
Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Beth H
Wilson/LAKE/PPRD/ABBOTT@ABBOTT, Judith S
Brownell/LAKE/PPRD/ABBOTT@ABBOTT, Katherine M
Landwer/LAKE/PPRD/ABBOTT@ABBOTT, Tawakol A
El-Shourbagy/LAKE/PPRD/ABBOTT@ABBOTT, Megan R
Hughes/LAKE/PPRD/ABBOTT@ABBOTT, Gary D
Jones/LAKE/PPRD/ABBOTT@ABBOTT, Howard S
Cheskin/LAKE/PPRD/ABBOTT@ABBOTT, Lloyd S
Dias/LAKE/PPRD/ABBOTT@ABBOTT, Rhonda J
Peck/LAKE/PPRD/ABBOTT@ABBOTT, Andrew C
Plasz/LAKE/PPRD/ABBOTT@ABBOTT, David G
Stroz/LAKE/PPRD/ABBOTT@ABBOTT, Diana L
Green/LAKE/PPRD/ABBOTT@ABBOTT, Walid
Awni/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep
Dutta/LAKE/PPRD/ABBOTT@ABBOTT, David C
Ross/LAKE/PPRD/ABBOTT@ABBOTT, David D
Morris/LAKE/PPRD/ABBOTT@ABBOTT, Charles
Locke/LAKE/PPRD/ABBOTT@ABBOTT, James W
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Yiming
Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Karen L
Cox/LAKE/PPRD/ABBOTT@ABBOTT, Joseph M
Machinist/LAKE/PPRD/ABBOTT@ABBOTT, Stanley A
Roberts/LAKE/PPRD/ABBOTT@ABBOTT, Jim J
Ciullo/LAKE/CAPD/ABBOTT@ABBOTT, John R
Donaubauer/LAKE/CAPD/ABBOTT@ABBOTT, Michael L
Branton/LAKE/PPD/ABBOTT@ABBOTT, Michael D
Meyer/LAKE/PPRD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, William M
Bracken/LAKE/PPRD/ABBOTT@ABBOTT, Julia Y
Hui/LAKE/PPRD/ABBOTT@ABBOTT, Teresita P
Curry/LAKE/PPRD/ABBOTT@ABBOTT, Laurie B

Confidential

ABBT245658



Corsi/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C
Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K
Waleska/LAKE/PPD/ABBOTT@ABBOTT, James
Steck/LAKE/PPRD/ABBOTT@ABBOTT, Linda M
Fisher/LAKE/PPRD/ABBOTT@ABBOTT, Steve
Szostak/LAKE/PPRD/ABBOTT@ABBOTT, Julie E
Debus-Levy/LAKE/PPRD/ABBOTT@ABBOTT, Susan
Boynton/LAKE/AV/ABBOTT@ABBOTT

cc:
Subject: ABT-594 Project Team Update



Michael K Biarnesen
10/09/2001 05:35 PM

To: Catherine K Kacos/LAKE/PPRD/ABBOTT@ABBOTT
cc:
Subject: ABT-594 Project Team Update

Dear Team,

As I communicated last month, there was a possibility that ABT-594 would be funded for a new Phase IIb study in 2002, but coming through the Budget Review meetings this week, the Global Pharmaceutical Executive Committee has decided that we will not move forward with the study. Based on this decision, we will discontinue efforts to manufacture fresh clinical supplies, and switch into a complete wrap-up mode.

Our next project team meeting is scheduled for Thursday, October 25 from 2:00 - 4:00 in AP52 Conference Room B. We will hold this meeting, and I ask that each of you review what activities you are involved in that need to be wrapped-up or discussed for continuation (i.e.: stability studies.) It is not clear at this time if ABT-594 will be put on the shelf, or be a candidate for outlicensing, so please be prepared with recommendations for either scenario.

If you have any questions before the team meeting, please feel free to give me a call or email

Thanks,

Mike Biarnesen
Operations Manager, Neuroscience Venture
Abbott Laboratories Global Pharmaceutical R&D
(847)938-6514 Fax: (847)938-5258

----- Forwarded by Michael K Biarnesen/LAKE/PPRD/ABBOTT on 10/09/01 05:23 PM -----

Michael K Biarnesen



Michael K Biarnesen
09/14/2001 02:15 PM

To: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T
Matakonis/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Carol J
Feige/LAKE/PPRD/ABBOTT@ABBOTT, Marian L
Borgstrom/LAKE/PPRD/ABBOTT@ABBOTT, Raymond A
Morales/LAKE/PPRD/ABBOTT@ABBOTT, Joan M
Freesht/LAKE/PPRD/ABBOTT@ABBOTT, Robert
O'Dea/LAKE/PPRD/ABBOTT@ABBOTT, Susan E
Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Beth H
Wilson/LAKE/PPRD/ABBOTT@ABBOTT, Judith S
Brownell/LAKE/PPRD/ABBOTT@ABBOTT, Katherine M
Landwehr/LAKE/PPRD/ABBOTT@ABBOTT, Tawakol A
El-Shourbagy/LAKE/PPRD/ABBOTT@ABBOTT, Megan R

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ABBT245659



Hughes/LAKE/PPRD/ABBOTT@ABBOTT, Gary D
 Jones/LAKE/PPRD/ABBOTT@ABBOTT, Howard S
 Cheskin/LAKE/PPRD/ABBOTT@ABBOTT, Lloyd S
 Dias/LAKE/PPRD/ABBOTT@ABBOTT, Rhonda J
 Peck/LAKE/PPRD/ABBOTT@ABBOTT, Andrew C
 Plaszi/LAKE/PPRD/ABBOTT@ABBOTT, David G
 Stroz/LAKE/PPRD/ABBOTT@ABBOTT, Diana L
 Green/LAKE/PPRD/ABBOTT@ABBOTT, Ji
 Zhou/LAKE/PPRD/ABBOTT@ABBOTT, Walid
 Awni/LAKE/PPRD/ABBOTT@ABBOTT, Sandeep
 Dutta/LAKE/PPRD/ABBOTT@ABBOTT, David C
 Ross/LAKE/PPRD/ABBOTT@ABBOTT, David D
 Morris/LAKE/PPRD/ABBOTT@ABBOTT, Charles
 Locke/LAKE/PPRD/ABBOTT@ABBOTT, James W
 Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Yiming
 Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Joseph M
 Machinist/LAKE/PPRD/ABBOTT@ABBOTT, Stanley A
 Roberts/LAKE/PPRD/ABBOTT@ABBOTT, Jim J
 Civillo/LAKE/CAPD/ABBOTT@ABBOTT, John R
 Donaubauer/LAKE/CAPD/ABBOTT@ABBOTT, Steve
 King/LAKE/PPRD/ABBOTT@ABBOTT, Michael L
 Branton/LAKE/PPD/ABBOTT@ABBOTT, Michael D
 Meyer/LAKE/PPRD/ABBOTT@ABBOTT, James
 Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, William M
 Bracken/LAKE/PPRD/ABBOTT@ABBOTT, Julia Y
 Hui/LAKE/PPRD/ABBOTT@ABBOTT, Teresita P
 Curry/LAKE/PPRD/ABBOTT@ABBOTT, Laurie B
 Corsi/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C
 Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Rosemarie K
 Waleska/LAKE/PPD/ABBOTT@ABBOTT, Susan
 Boynton/LAKE/AL/ABBOTT@ABBOTT, Danhui
 Wang/LAKE/PPD/ABBOTT@ABBOTT, Steve
 Szostak/LAKE/PPRD/ABBOTT@ABBOTT
 cc: Nancy M Palbicki/LAKE/PPRD/ABBOTT@ABBOTT, Selia T
 Patterson/LAKE/PPD/ABBOTT@Abbott
 Subject: 09/20 ABT-594 Project Meeting

Next week's ABT-594 project meeting is cancelled.

As you may have heard, we had our executive review with Jeff Leiden, et al. on Monday, and he has asked us to evaluate the costs, time and probabilities of success of a new study. In general, this is better news than expected, since the odds-makers had us preparing our horse for the glue factory. For the 2002 planning process, we are still assumed to be unfunded, but there is a chance that we will be back in the race for funding once the preliminary cost and time for a Phase IIb, Part 2 study are reviewed with Jeff. If we get a positive read, a new team meeting will be convened to discuss the study design and critical issues. Please bear with us as we wait to see if there is a miraculous resurrection for this program!

Mike B

Confidential

ABBT245660

McCarthy Deposition Exhibit 60

P's Exhibit HM

Philip M
Deemer/LAKE/CORP/A
BBOTT

10/19/2001 01:31 PM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT


cc:

bcc:

Subject: Re: ABT-594 Call

Thank you Bruce, I will handle.

Phil
Bruce McCarthy

 Bruce McCarthy
10/19/01 12:06 PM

To: Philip M Deemer/LAKE/CORP/ABBOTT@ABBOTT
cc:
Subject: ABT-594 Call

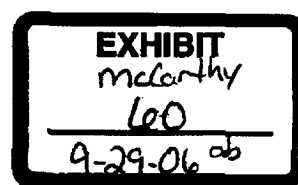
Phil-

Received a call (voice mail) from Tom Lenz, Bayer Animal Health, 913-268-2591, inquiring about outlicense of 594. Do you want to handle these? We have a meeting next week to discuss a bit more, but thought you might want to be the point of contact for these kinds of inquiries. I've not returned his call--let me know if you would like me to get more info.

Bruce.

Confidential

ABBT245857



McCarthy Deposition Exhibit 61

D's Exhibit 1113

Philip M
Deemer/LAKE/CORP/ABBO
TT
10/23/2001 02:58 PM

To: Ake L. Johansson/LAKE/CORP/ABBOTT@ABBOTT
cc
bcc
Subject: Re: Non-confidential briefing on ABT-594

This is a list of companies we brainstormed yesterday as potential candidates for ABT 594. I am preparing a non-confidential package and we have good confidential materials already.

----- Forwarded by Philip M Deemer/LAKE/CORP/ABBOTT on 10/23/01 02:57 PM -----

Bruce McCarthy
10/23/01 09:24 AM

To: Philip M Deemer/LAKE/CORP/ABBOTT@ABBOTT
cc: James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: Non-confidential briefing on ABT-594

will send my comments by fax (had printed out your file and edited)--let me know if you're unable to read the comments.

Your document (with the competition section) got me thinking to add a few more potential companies:

Purdue
J&J
Targacept
Icagen
Elan
Mallinkrodt
TAP
Takeda
Endo
Adolor
Pain Therapeutics
Sepracor
Pfizer
Lundbeck
Sanofi-Synthelabo
AstraZeneca
GSK
Boehringer Ingelheim
Novartis
Aventis
Esteve
Cambridge Neuroscience
Taisho

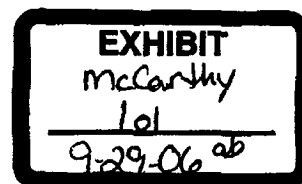
Philip M Deemer

Philip M Deemer
10/22/2001 04:30 PM

To: James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K Biommesen/LAKE/PPRD/ABBOTT@ABBOTT, Danhui Wang/LAKE/PPD/ABBOTT@ABBOTT
cc:
Subject: Non-confidential briefing on ABT-594

Confidential

ABBT246791



The attached is what we used for Hancock as the conf disclosure. Pls. suggest revisions so that we can use this as a non-confidential disclosure.

Thank you.



ABT-594 201.doc

Confidential

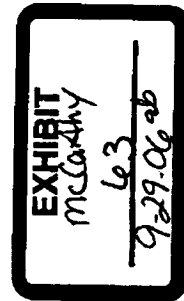
ABBT246792

McCarthy Deposition Exhibit 63

P's Exhibit HP

ABT-594

**PEC Review Book:
Proposal for additional
study and background
(Nonstandard format)**



ABT-594 Proposal for additional Phase IIb study

- Evaluate efficacy and tolerability at “intermediate doses”: 75-125 mcg BID
 - Prior studies evaluated 25-75 mcg BID and 150-300 mcg BID
 - Tolerability
 - 75 mcg BID tolerability is potentially acceptable
 - 150-300 mcg BID tolerability is unacceptable
 - Efficacy
 - Upside: dose response may be relatively flat at doses tested to date and doses between 75 and 125 mcg BID could provide clinically meaningful neuropathic pain relief
 - Downside: limited sample size in prior study at 75 mcg BID may mean that true efficacy, if toward the lower bound of confidence intervals, may not be clinically meaningful at doses between 75 and 125 mcg BID

September 27, 2001

2

ABT-594 Intermediate Dose Phase IIb Study: Preliminary Design

- Placebo-controlled, double-blind, randomized, parallel design trial, 8 weeks
- Diabetic neuropathic pain
- N=160, randomized 1:1 to either placebo or ascending doses of ABT-594
 - Titrate all patients to 75 mcg BID from 25 mcg BID between Day 1 and Day 5
 - Patients who are tolerating drug (75 mcg BID) may increase another 25 mcg BID on Day 12 (to total dose 100 mcg BID)
 - Patients who are tolerating drug may increase another 25 mcg BID on Day 19 (total dose may be either 100 or 125 mcg BID, depending on whether a patient also increased dose on Day 12)
 - If a patient does not tolerate an increase in dose, their dose will be lowered back down (but not lower than 75 mcg BID)

September 27, 2001

3

ABT-594 Intermediate Dose Phase IIb Study: Preliminary Design

- Primary endpoint
 - Diary-based 11-point Likert pain rating scale (same as prior study)
 - Secondary endpoints:
 - 11-point Likert pain rating scale at site visits
 - SF-MPQ
 - SF-36
- PK
 - Population and intensive for pharmacodynamics
 - Attempt to collect when “important” AEs occur
 - Nausea, vomiting or dizziness leading to discontinuation
- Low to medium precision ECG for QT evaluation

Highly Confidential

September 27, 2001

ABBT113288.UR

ABT-594 Intermediate Dose Phase IIb Study: Rationale for Design

- Maximize tolerability by slowly ascending dose
- Provide alternative to discontinuation by allowing for dose reduction if dose escalation is not tolerated
- 125 mcg BID dose ceiling should prevent intolerability
- Under condition of dose ceiling, maximize efficacy by permitting patients to increase dose based upon tolerability alone
- Subjects will be exposed to a minimum dose (75 mcg BID) for almost 8 weeks
- Subjects may be exposed to 100 mcg BID for almost 7 weeks and 125 mcg BID for almost 6 weeks
 - Most patients expected to achieve 100 or 125 mcg BID
- Well-powered study
- Design similar to Gabapentin trial for neuropathic pain

September 27, 2001

ABT-594 Intermediate Dose Phase IIb Study: Timeline (assumes most of funding starting Jan 2002)

Approved protocol	1/2002
CRO contract signed	1/2002
Investigator Meeting	4/2002
1st subject dosed	5/2002
Last Subject/Last Dose	2/2003
Randomization Schedule Release	4/2003

Fully burdened internal and external costs (\$MM)

2001	2002	2003	Total
0.085	3.760	0.855	4.700

September 27, 2001

ABT-594 Intermediate Dose Phase IIb Study: Timeline (Upside for earlier release of funds)

Approved protocol	11/2001
CRO contract signed	12/2002
Investigator Meeting	3/2002
1st subject dosed*	4/2002
Last Subject/Last Dose	1/2003
Randomization Schedule Release	3/2003

Fully burdened internal and external costs (\$MM)

2001	2002	2003	Total
0.285	3.660	0.755	4.700

*Upside scenario is not significantly different with respect to date of study start because clinical supplies are rate limiting

September 27, 2001

ABT-594 Intermediate Dose Phase IIb Study: Cost Details (assumes most of funding starting Jan 2002)

	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>Total</u>
• Clinical supply manufacture	0.085	0.045		0.130
• Clinical supply packaging		0.165		0.165
• Investigator meeting		0.140		0.140
• Clinical study		2.500	0.460	2.960
• IVRS & clinical shipping		0.100	0.025	0.125
• Drug analysis		0.175	0.075	0.250
• DM / Stats support		0.125	0.125	0.250
• PK support		0.050	0.030	0.080
• Venture Staff (2 FTE)		0.360	0.090	0.450
• Other support groups		0.100	0.050	0.150
Total:	0.085	3.760	0.855	4.700

September 27, 2001

8

ABT-594 Intermediate Dose Phase IIb Study: Cost Details (Upside for earlier release of funds)

	<u>2001</u>	<u>2002</u>	<u>2003</u>	<u>Total</u>
• Clinical supply manufacture	0.085	0.045		0.130
• Clinical supply packaging		0.165		0.165
• Investigator meeting		0.140		0.140
• Clinical study	0.200	2.400	0.360	2.960
• IVRS & clinical shipping		0.100	0.025	0.125
• Drug analysis		0.175	0.075	0.250
• DM / Stats support		0.125	0.125	0.250
• PK support		0.050	0.030	0.080
• Venture Staff (2 FTE)		0.360	0.090	0.450
• Other support groups		0.100	0.050	0.150
Total:	0.285	3.660	0.755	4.700

September 27, 2001

9

ABT-594: Development Timelines

Data Available from new Phase IIb Trial
Start Phase III
NDA Submit
Approval

2Q2003
4Q2003
3Q2005
3Q2006

Year	Cost (\$MM)
2001	0.085
2002	3.760
2003	25.203
2004	40.720
2005	24.508
2006	11.639

September 27, 2001

10

ABT-594

Background

11

ABT-594's Potential for Pain Relief

- Efficacy across preclinical models of pain
 - Efficacy of morphine without morphine-like adverse events
 - Efficacy in neuropathic pain
- Commercial and clinical development plan targeted acute and chronic nociceptive pain and neuropathic pain, based upon preclinical promise
- Tolerability/onset of action issues made neuropathic pain relatively more attractive
 - Dosages that provide meaningful acute relief of pain are not well tolerated
 - Titration not well suited to intermittent use, as seen with most chronic nociceptive pain
 - Titration is used with all currently available drugs for neuropathic pain

September 27, 2001

12

Phase IIb Study in Neuropathic Pain (M99-114)

Study Results

- Summary
- Neuropathic pain reminder
- Study Design
- Efficacy Results
- Adverse Events
- Conclusions and Options

September 27, 2001

13

Phase IIb Study in Neuropathic Pain (M99-114)

Summary

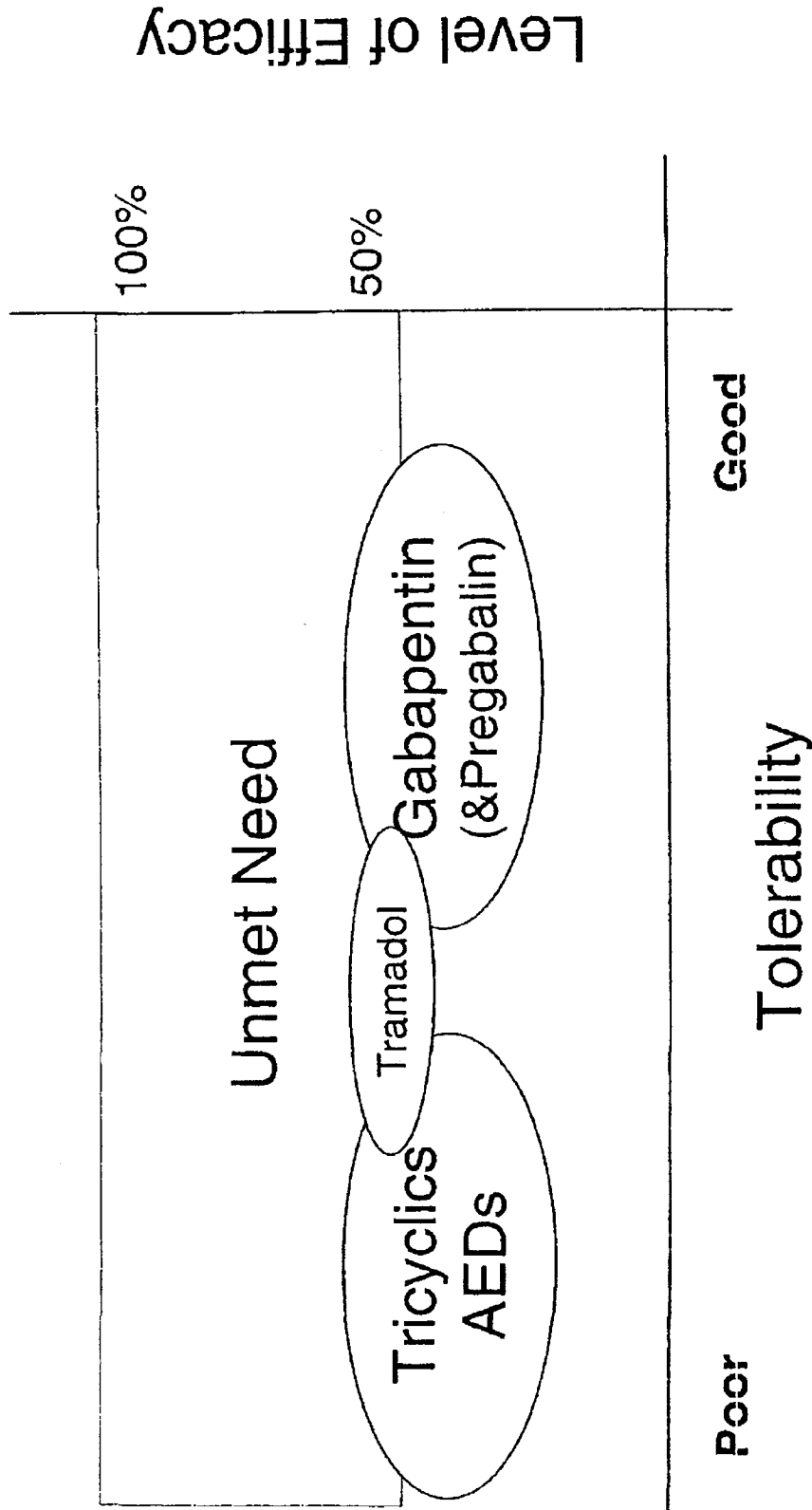
- **EFFICACY**
 - **150, 225 and 300 mcg BID are significantly better than placebo** as measured by the primary efficacy variable (reduction in daily pain)
 - ITT Analysis: 29-30% vs. 17% placebo
 - Gabapentin: 39% vs. 22% placebo
 - Completer Analysis: 38-48% vs. 18% placebo
 - Responder rates: 26% (ITT), 47% (Completer)
 - Greater mean pain reduction and responder rates in site-based pain measurements
- **TOLERABILITY & SAFETY**
 - Dose dependent increase in nausea, vomiting, dizziness
 - Nausea: 34-46% • Dizziness: 17-28%
 - Vomiting: 15-21% • Abnormal Dreams: 18-22%
 - Significant Discontinuation Rate: 66% due to AE at 300 mcg BID

September 27, 2001

14

Neuropathic Pain Reminder

Treatment



September 27, 2001

15

Neuropathic Pain Market

	2000 Rx (MM)	2000 sales (\$MM)	Rx CAGR (96-2000)	Sales CAGR (96- 2000)
Total:				
US	10.6	\$470	6%	45%
Ex-US	18.1	\$235	11%	24%
Gabapentin:				
US	3.9	\$352	80%	94%
Ex-US	1	\$42	125%	191%

Source: Decision Resources; IMS factored analysis

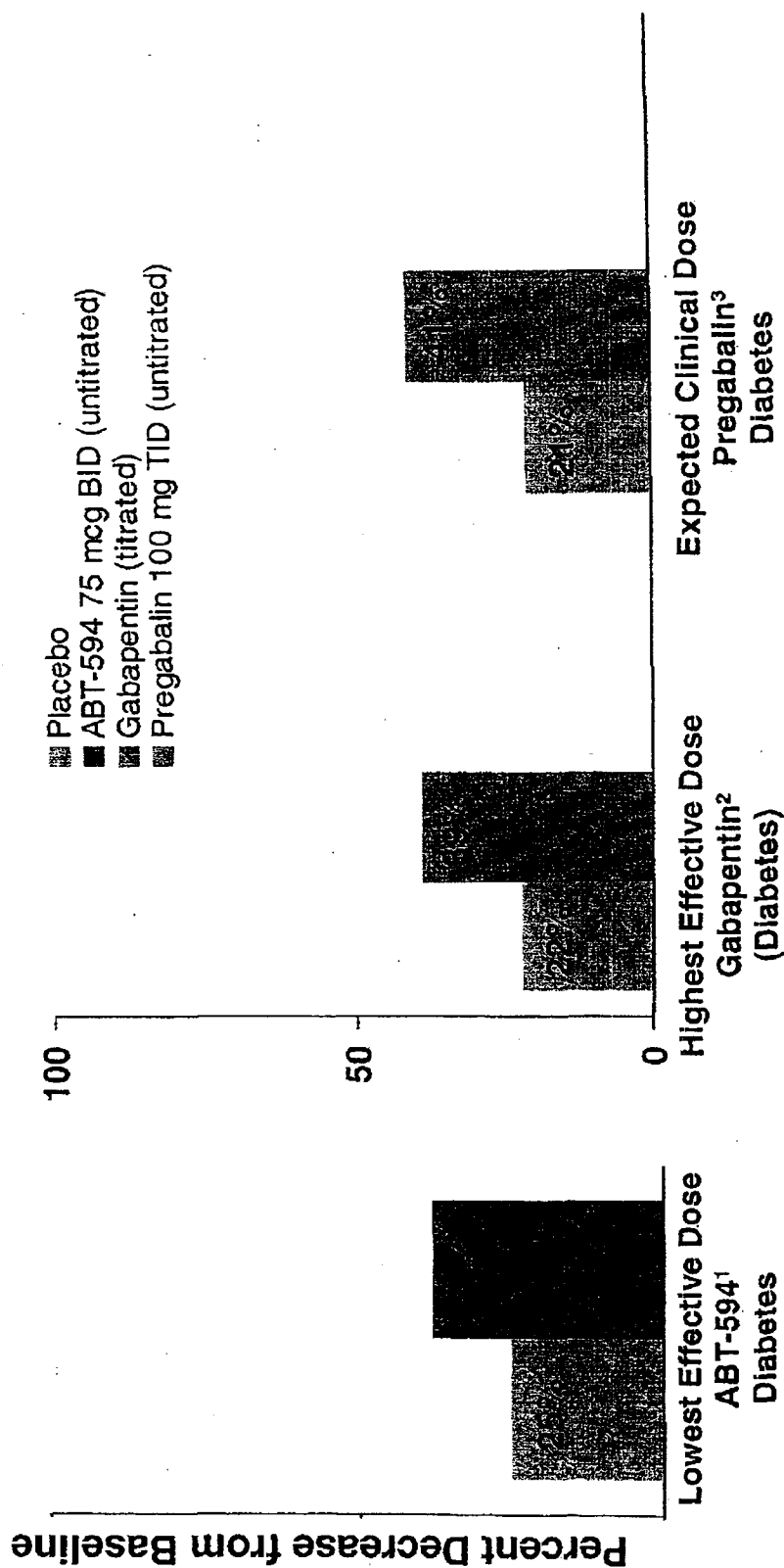
- Growth of sales for neuropathic pain agents exceeds Rx growth:
 - Driven by continued growth of the branded and premium priced gabapentin (Neurontin), at the expense of other anti-epileptics and generic tricyclic antidepressants.

September 27, 2001

16

Phase IIa: ABT-594 75 mcg BID had a similar effect to gabapentin

ABT-594 vs. Gabapentin and Pregabalin



1 4-point categorical scale final vs. baseline
 2 11-point Likert Scale week 8 vs. baseline
 3 11-point Likert scale week 5 vs. baseline

September 27, 2001

Phase IIa: ABT-594 75 mcg BID untitrated was relatively well tolerated

Event	Amitriptyline 150 mg/d ¹	Carbamazepine 600 mg/d	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 ² 75 mcg BID
Confusion	N/A	N/A	8%	5%	0%
Somnolence	66%	53%	23%	24%	0%
Dizziness	28%	40%	24%	27%	7%
Nausea	N/A	7%	8%	N/A	15%
Vomiting	N/A	N/A	N/A	N/A	5%
Peripheral edema	N/A	N/A	N/A	7%	1%
Constipation	14%	N/A	N/A	N/A	N/A
Dry mouth	90%	N/A	N/A	N/A	N/A
Instability	N/A	13%	N/A	N/A	

¹ Max, 1987 (n=29)

² M98-826 and M98-833 combined

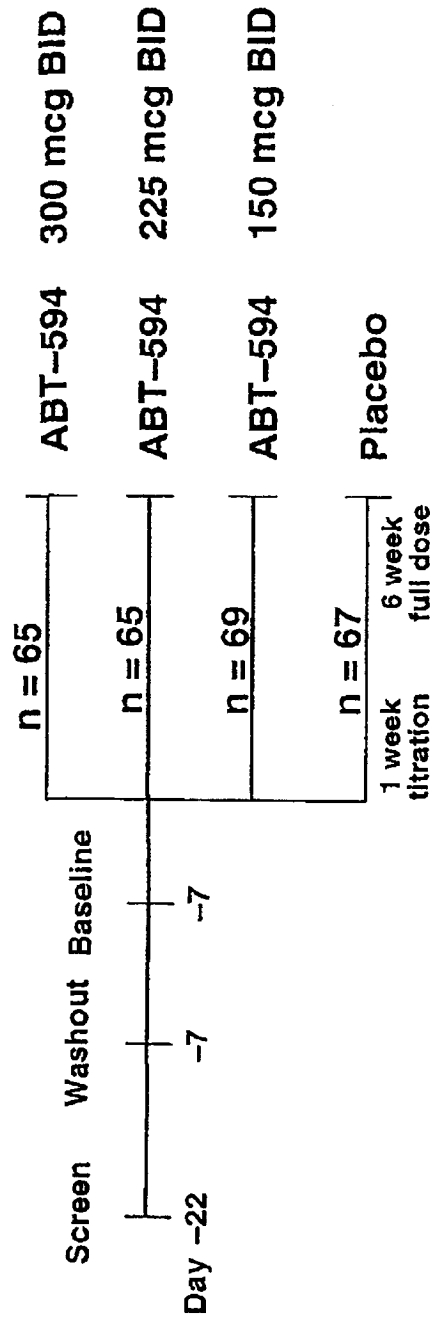
N/A - Not Available

September 27, 2001

Phase IIb Study in Neuropathic Pain (M99-114)

Design

- 266 patients (320 planned), randomized, double-blind, placebo-controlled, multiple dose

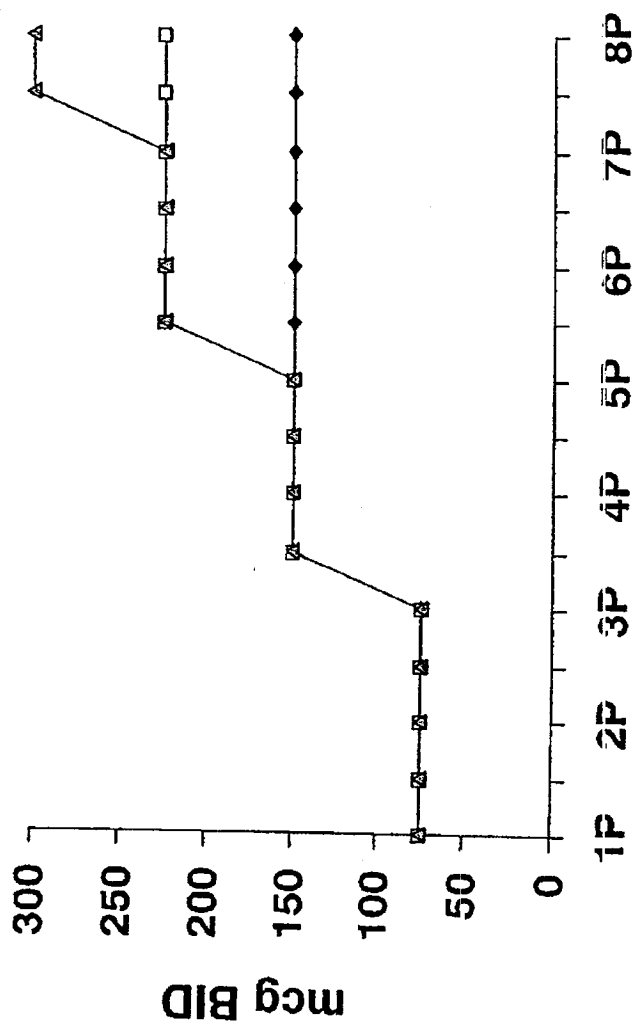


- Diabetic polyneuropathy
- 7-day titration phase; treatment visits at 2, 3, 5 and 7 weeks
- Power
 - Planned: 80% for ES 0.46 with 80/group
 - Study: 60% for ES 0.46 with 56/group (ES 0.65 for site-based pain rating scale)
- Concomitant analgesics disallowed

September 27, 2001

M99-114 Dose Titration Schedule

- ◆ ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- △ ABT-594 300 mcg BID



Study Day (P=PM dose)

September 27, 2001

Premature Terminations increased with increasing doses of ABT-594

Subject Disposition

Reason for Discontinuation	Placebo	% of Subjects Discontinuing ABT-594		
		150 mcg BID	225 mcg BID	300 mcg BID
Adverse Event	9	28	46	66
Lack of Efficacy	9	9	3	7
Lost to Follow-up	0	0	1	3
Withdrew Consent	3	5	9	7
Other	2	2	4	3
Total Discontinuation	22	38	57	75

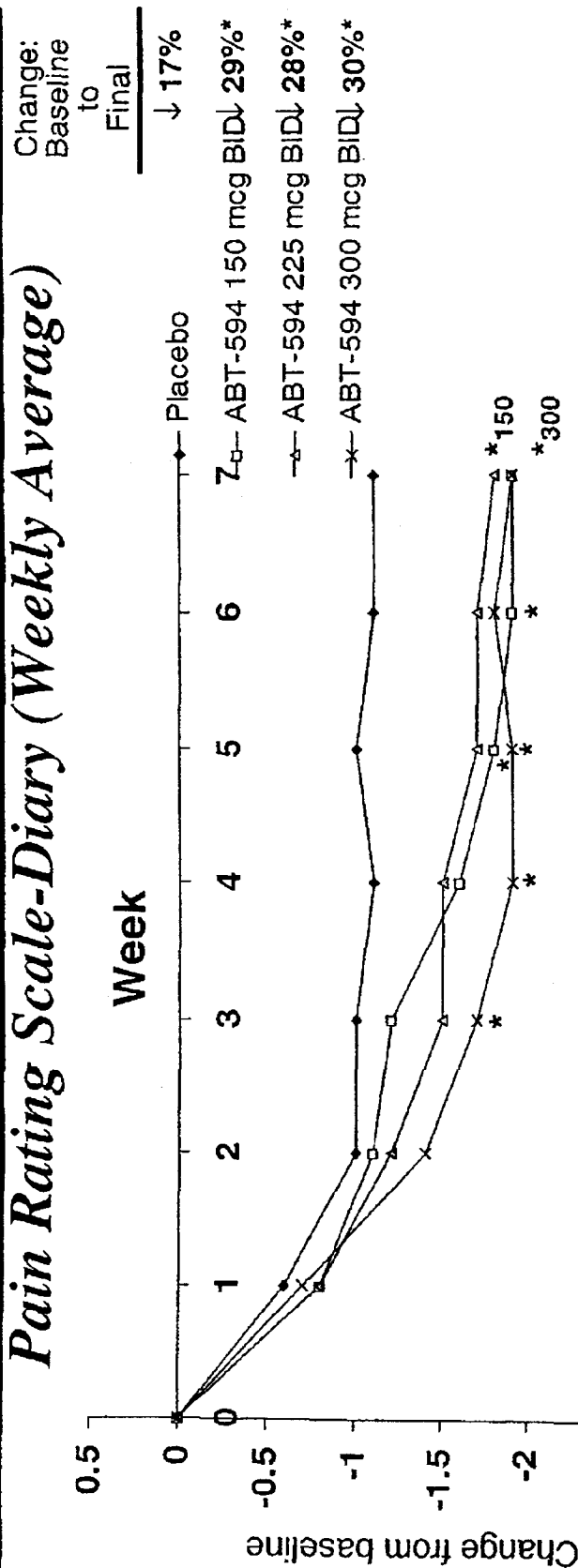
Percents may not sum correctly due to rounding

September 27, 2001

21

ABT-594 150, 225, & 300 mcg BID reduced pain significantly vs. placebo as measured by the primary efficacy variable: intent to treat population

Pain Rating Scale-Diary (Weekly Average)



N% at week 7

Placebo	89%
ABT-594 150 mcg BID	86%
ABT-594 225 mcg BID	84%
ABT-594 300 mcg BID	79%

*p<0.05

Maximum possible decrease for 150 mcg BID group was 6.6

September 27, 2001

22

Completer analysis may predict upside potential of ABT-594

ITT

More rigorous evaluation
of study results

Completer

Potential to predict
upside of efficacy if all
patients were able to
complete study

Advantages

Disadvantages

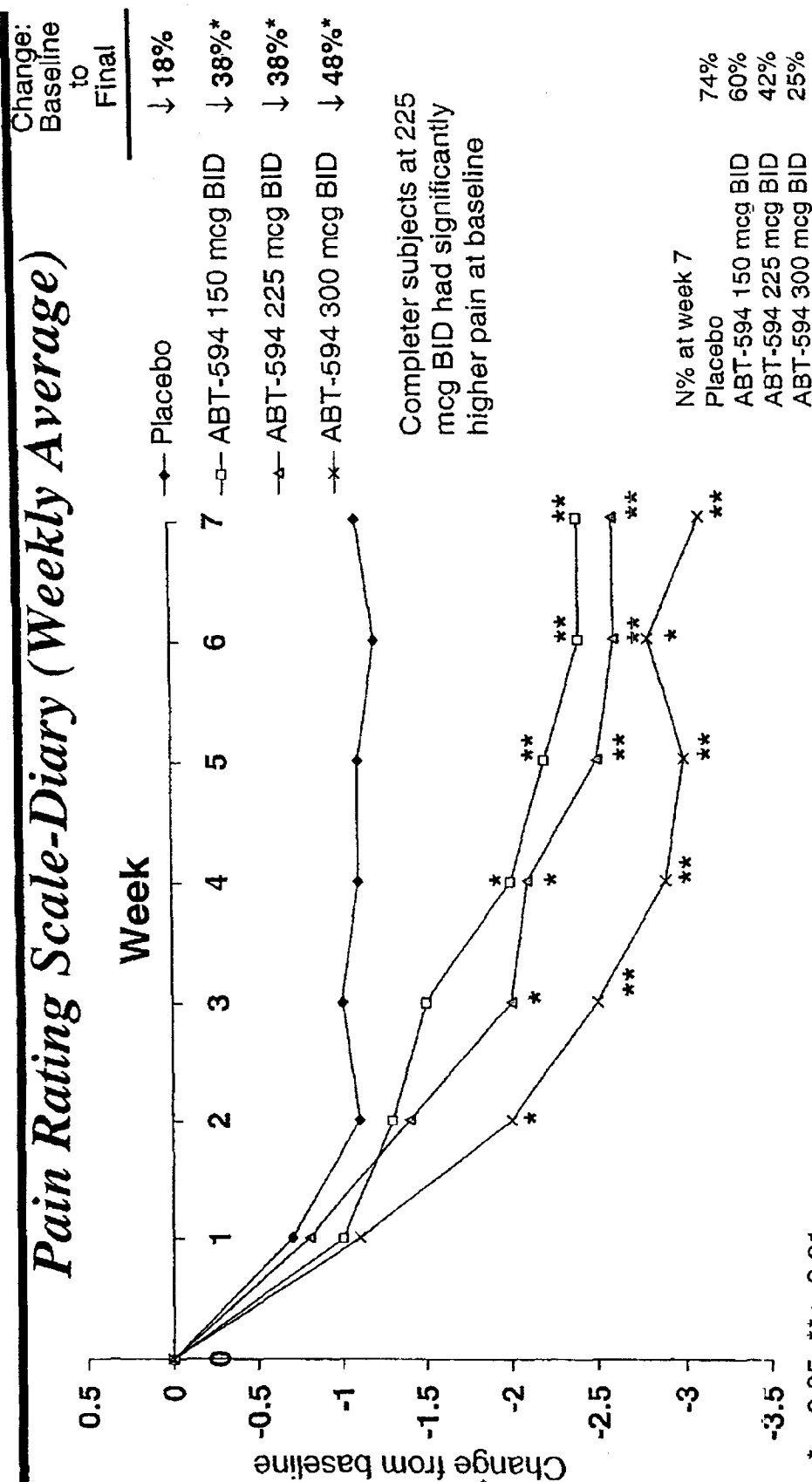
Handicapped prediction
of upside potential of
efficacy given high
discontinuation rate
(especially early)

Patients who completed
the Phase IIb study may
not predict accurately
efficacy if all patients
could tolerate ABT-594

September 27, 2001

23

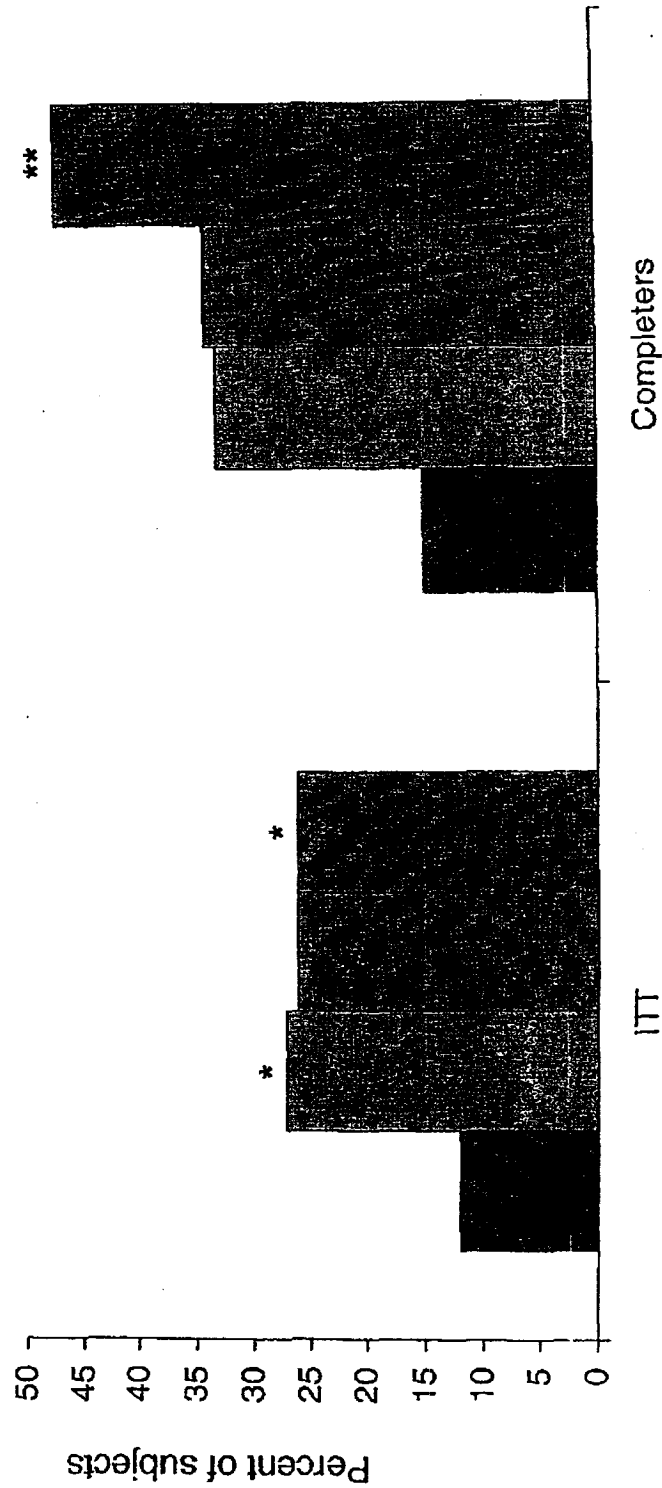
ABT-594 150, 225, & 300 mcg BID reduced pain significantly vs. placebo as measured by the primary efficacy variable: subjects who completed study



Responder Rates 50% or greater improvement

Pain Rating Scale-Diary

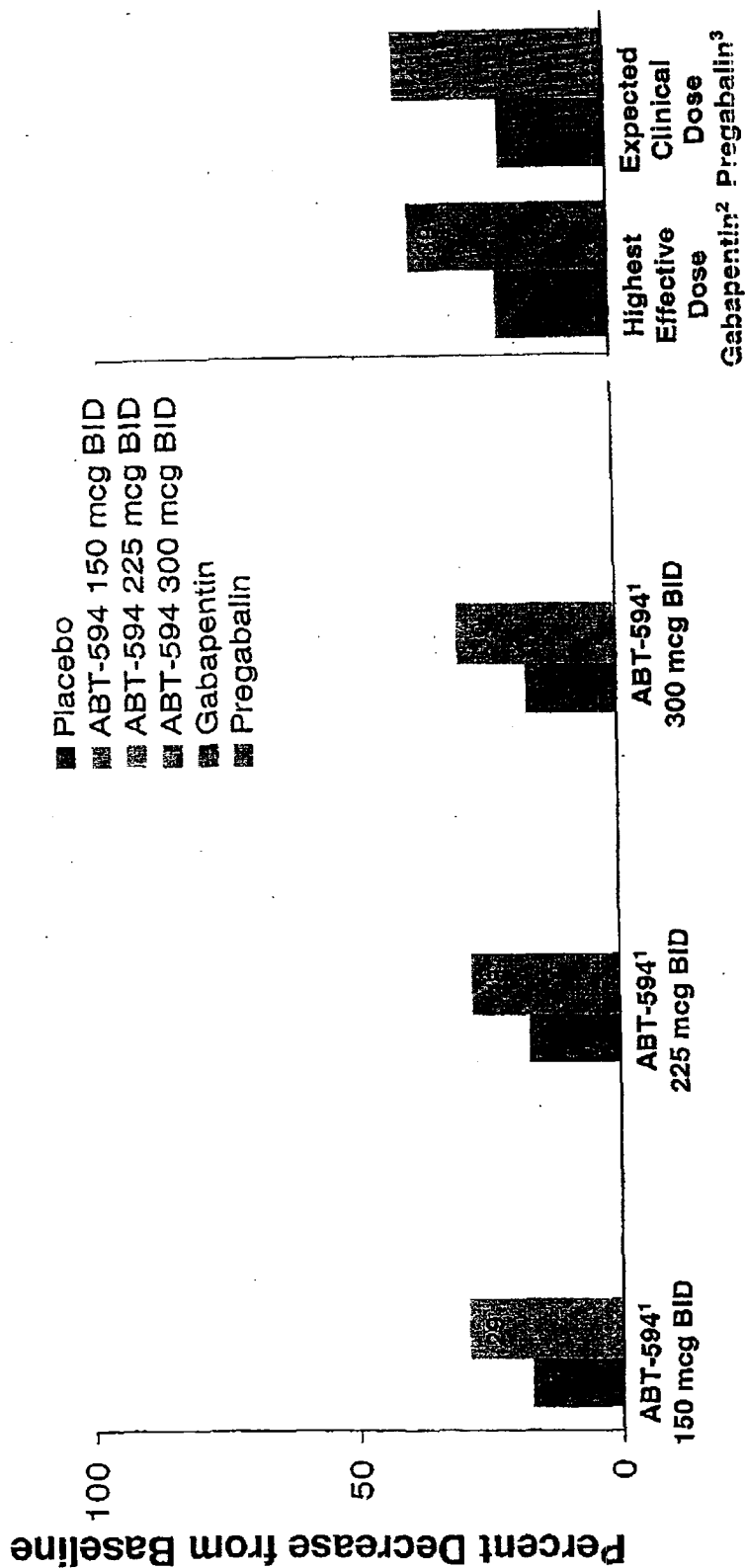
- Placebo
- ABT-594 150 mcg BID
- ABT-594 225 mcg BID
- ABT-594 300 mcg BID



September 27, 2006
ITT
*p<0.05, **p<0.01 vs. placebo

ABT-594 150, 225, 300 mcg BID may reduce diabetic neuropathic pain more than gabapentin or pregabalin

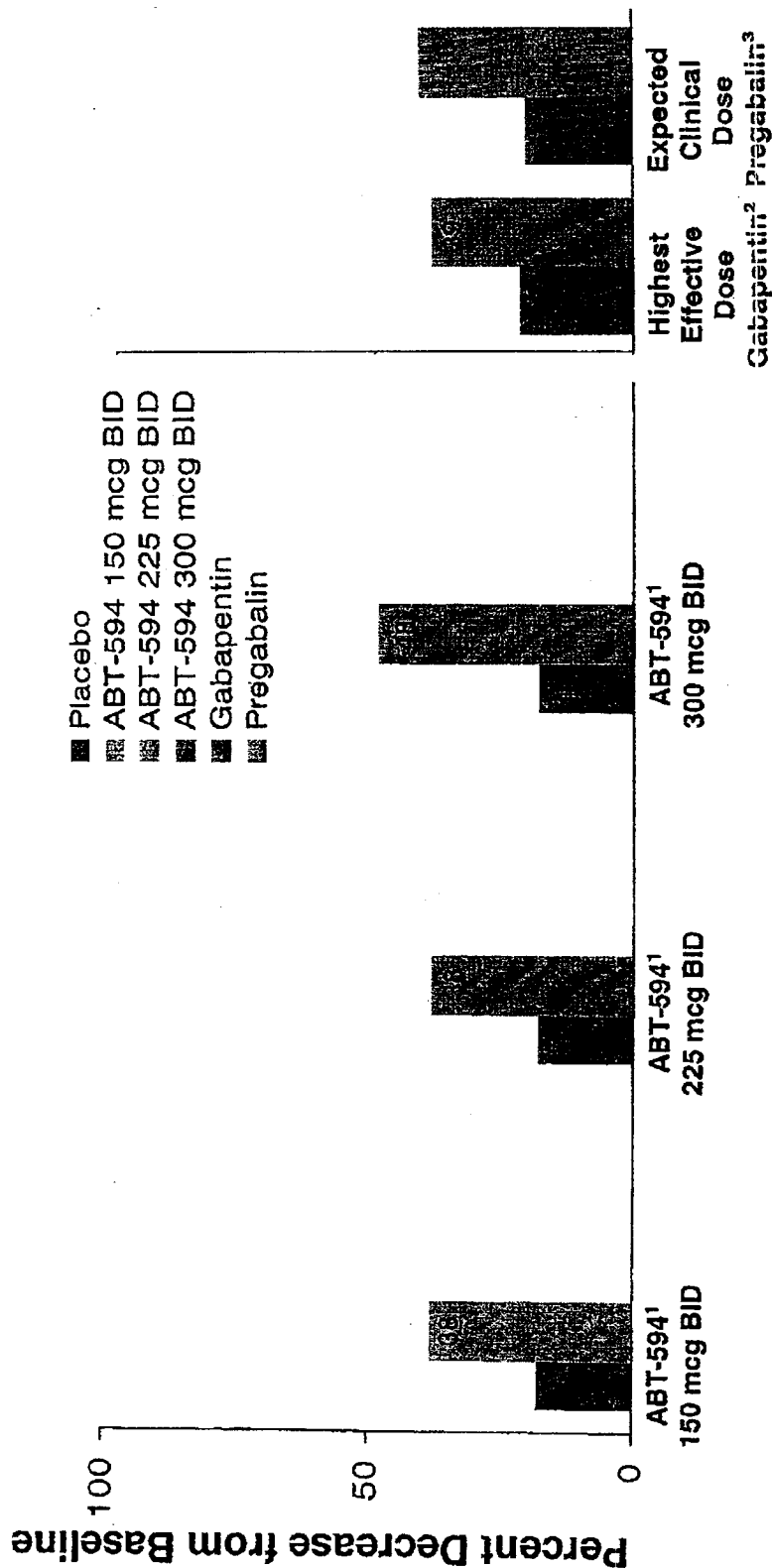
ABT-594 ITT vs. Gabapentin and Pregabalin



September 27, 2001

ABT-594 150, 225, 300 mcg BID may reduce diabetic neuropathic pain more than gabapentin or pregabalin

ABT-594 Completers vs. Gabapentin and Pregabalin



¹ 11-point Likert scale week 7 vs. baseline
² 11-point Likert scale week 8 vs. baseline
³ 11-point Likert scale week 5 vs. baseline

September 27, 2001

Adverse Event Rates for Select Analgesics

Event	Amitriptyline 150 mg/d ¹	Gabapentin 3600 mg/d	Pregabalin 300 mg/d	ABT-594 150 mcg BID	ABT-594 300 mcg BID
Confusion	N/A	8%	5%	0%	1%
Somnolence	66%	23%	24%	2%	0%
Dizziness	28%	24%	27%	17%	28%
Nausea	N/A	8%	N/A	34%	46%
Vomiting	N/A	N/A	N/A	15%	21%
Peripheral edema	N/A	N/A	7%	0%	0%
Constipation	14%	N/A	N/A	3%	7%
Dry mouth	90%	N/A	N/A	3%	1%

¹ Max, 1987 (n=29)
N/A - Not Available

September 27, 2001

28

**Efficacy and safety did not vary consistently by
subject characteristics**

- Smoker/Non-smoker
- Male/Female
- Weight
- Age
- Renal Function

September 27, 2001

29

ABT-594 150, 225 and 300 mcg BID were not associated with clinically meaningful changes in vital signs, ECGs or laboratory data

- Vital signs
- ECG
- Laboratory data

September 27, 2001

30

Phase IIb Study in Neuropathic Pain (M99-114)

Conclusions

- ABT-594 significantly reduces diabetic neuropathic pain
- ABT-594, as administered without additional improvements in tolerability, has a narrow therapeutic window
- Intermediate doses (75-125 mcg BID) may be associated with clinically meaningful efficacy and acceptable tolerability
- Future subtype selective NNRs for pain may provide meaningful pain relief across all pain types with an acceptable therapeutic window

September 27, 2001

31

McCarthy Deposition Exhibit 66

P's Exhibit BW



Gary D
Jones/LAKE/PPRD/ABBOTT

10/30/1999 06:25 PM

To: Tamara L Garavalia/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject: meeting

Tamara,
you should be primary representative for the clinical trials team meeting. Please reply to Bruce and make sure both of us are on the list.

Thanks

Gary

----- Forwarded by Gary D Jones/LAKE/PPRD/ABBOTT on 10/30/99 06:22 PM -----

Bruce McCarthy 10/29/99 06:07 PM

To: Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT, Diane M Barnes/LAKE/PPRD/ABBOTT@ABBOTT, Peter D Bryan/LAKE/PPRD/ABBOTT@ABBOTT, Howard S Cheskin/LAKE/PPRD/ABBOTT@ABBOTT, Julie E Debus-Levy/LAKE/PPRD/ABBOTT@ABBOTT, Susana K Dennis/LAKE/PPRD/ABBOTT@ABBOTT, Lloyd S Dias/LAKE/PPRD/ABBOTT@ABBOTT, Michael A Dote/LAKE/PPRD/ABBOTT@ABBOTT, James T Doran/LAKE/PPRD/ABBOTT@ABBOTT, Tawakol A El-Shourbagy/LAKE/PPRD/ABBOTT@ABBOTT, Tamara L Garavalia/LAKE/PPRD/ABBOTT@ABBOTT, Julie V Jarvis/LAKE/PPRD/ABBOTT@ABBOTT, Gary D Jones/LAKE/PPRD/ABBOTT@ABBOTT, Katherine M Landwer/LAKE/PPRD/ABBOTT@ABBOTT, Lillian L Lee/LAKE/PPRD/ABBOTT@ABBOTT, Rhonda J Peck/LAKE/PPRD/ABBOTT@ABBOTT, Nigel Livesey/LAKE/PPRD/ABBOTT@ABBOTT, Charles Locke/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, Susan E Nunn/LAKE/PPRD/ABBOTT@ABBOTT, Robert ODea/LAKE/PPRD/ABBOTT@ABBOTT, Laura Robinson/LAKE/PPRD/ABBOTT@ABBOTT, David C Ross/LAKE/PPRD/ABBOTT@ABBOTT, Russell T Slade/LAKE/PPRD/ABBOTT@ABBOTT, James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Azza M Wagdy/LAKE/PPRD/ABBOTT@ABBOTT, Raymond C Wieboldt/LAKE/PPRD/ABBOTT@ABBOTT, Bath H Wilson/LAKE/PPRD/ABBOTT@ABBOTT, Yiming Zhang/LAKE/PPRD/ABBOTT@ABBOTT, Xavier Frapaise/LAKE/PPRD/ABBOTT@ABBOTT

cc: Marilyn J Collicott/LAKE/PPRD/ABBOTT@ABBOTT, Rita M Driscoll/LAKE/PPRD/ABBOTT@ABBOTT, Carol J Felge/LAKE/PPRD/ABBOTT@ABBOTT, Kevin J Heuser/LAKE/PPRD/ABBOTT@ABBOTT, Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT, Fred W Siebert/LAKE/PPRD/ABBOTT@ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Mary E Smith/LAKE/PPRD/ABBOTT@ABBOTT, Jerri L Swerdlow/LAKE/PPRD/ABBOTT@ABBOTT, Joan M Penn/LAKE/PPRD/ABBOTT@ABBOTT

Subject:

This email is being sent to introduce several changes in the way meetings for the ABT-594 project are organized and introduces the ABT-594 Clinical Trials Team Meetings. This email is being sent to people who will attend the new Clinical Trials Team Meeting and the continuing Clinical Supplies Meeting (you may not be attending both, however).

ABT-594 Clinical Trials Team Meetings

The goal of the new monthly Clinical Trials Team (CTT) Meeting will be to review the status of ongoing clinical trials and plan for future clinical trials. This meeting will be strategic and decision-making in nature in order to address the following issues:

1. What is the status of ongoing clinical trials?
2. Are current and planned clinical trials on-target (time and cost) and coordinated to achieve current goals (through NDA and beyond)? Are all prerequisites for the initiation and completion of each study identified and coordinated (details to be addressed in individual study meetings-see below)?
3. Do past, present and planned clinical trials (phase I-IV) achieve registration and commercial

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objectives worldwide? If no, which trials should not proceed and what trials should be added to the plan?

The status of clinical trials will be communicated monthly by electronic distribution of minutes to everyone involved with the conduct and support of ABT-594 clinical trials. In addition to minutes, Gantt's will be updated.

The CTT Meeting will take place approximately one week prior to the ABT-594 Product Development Team (PDT) Meeting. Some of you will have received an email about the PDT Meeting. The PDT Meeting will address *operational* issues related to the successful completion of the NDA and beyond. The CTT Meeting will focus on strategy and implementation of the clinical program. Updates and outcomes from the CTT Meeting will be brought to the PDT Meeting as a single item on the PDT Meeting agenda. More focused meetings, such as the Phase IIb Meeting described below, will address highly detailed issues such as patient enrollment, query resolution, CRF flow, drug resupply, etc, for a small group of studies.

In order to facilitate active discussion, the CTT Meeting needs to be limited to decision-making representatives from the following departments: Statistics, Data Management, PK/Drug Analysis, PPD Regulatory, PPD RQA, PPD Commercial, AI Commercial-as needed, AI Regulatory-as needed, AI Medical-as needed, Clinical Pharmacology-as needed, Venture (Silber, McCarthy, Driscoll, Collicott, Siebert, Matalonis, Swerdlow, Heuser, Smith, Kacos, Perri, Feige). Another meeting, the Clinical Supplies Meeting, will continue to serve as a forum to address all of the issues involved in supplying a clinical study with study drug. Aldona Matalonis will serve as the link between the CTT Meetings and the Clinical Supplies Meetings.

Please identify a primary representative to attend the monthly CTT Meeting and a back-up representative (for when the primary is unavailable) from your area. Forward that information (along with your department name and function) to Cathy Kacos.

Once we have received the attendee list, we will notify you of the meeting time and place (the first meeting is anticipated to occur in the second week of November, 1999). Marilyn Collicott (Analgesia Venture) will be responsible for the agenda. The meeting will last between one and two hours. If additional time is required for discussion, break-out meetings will be scheduled (and decisions from these break-out meetings will be reviewed at the next CTT meeting).

Finally, please provide an updated list for anyone and everyone working on ABT-594 in your area. Cathy Kacos (Analgesia Venture) will maintain this Clinical Trial Team list (the list will be used for distribution of minutes and news). *Please provide this information whether you will be attending the CTT meeting or the Clinical Supplies Meeting.*

This new meeting represents an experiment. Please feel free to comment on any aspect of the structure and function of this meeting so that the goal of the most efficient exchange of information can be achieved.

Additional ABT-594 meetings:

ABT-594 Product Development Team Meeting

Once-a-month (mid-month).

Primary representative from CAPD, PARD, Regulatory (PPD and AI), Commercial (PPD and AI), AI Medical, Drug Safety, Finance, Discovery, Operations, Venture (Silber, McCarthy, Driscoll, Collicott, Matalonis, Kacos).

Goal: Each department will review activities and plans. Project goals and milestones will be assessed and updated. Critical paths and issues will be identified and addressed.

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Agenda Contact Collicott

Outputs: Minutes, break-out meetings, updated project Gantt. Monthly Project Status Report. Minutes will be distributed to entire ABT594 project team.

ABT-594 Phase IIb Meeting (M99-114, M99-115)

Once-a-week (once-a-month this meeting is the same meeting as Clinical Trials Team Meeting).

Venture representatives (Silber, McCarthy, Collicott, Siebert, Matalonis, Swardlow, Heuser, Smith, Kacos, Perri, Feige), statistics, data management, CRO managers

Goal: Review the status of M99-114 and M99-115 in detail. Address issues to achieve goals.

Agenda Contact Siebert/Swardlow

Outputs: Updated study Gantt.

Clinical Supplies Meeting

Once-a-month (to follow Clinical Trials Meeting)

Venture representatives (Matalonis, Feige, study representative as needed), PARD (formulation, analytical, stability as needed, positive controls as needed), IDQA, IDS, PPD Regulatory as needed, AI Regulatory as needed

Goal: Logistics (detail) for study drug supplies.

Agenda Contact Matalonis.

Output: Minutes (distributed to Clinical Trial Team).

Bruce.

McCarthy Deposition Exhibit 67

P's Exhibit BZ



Christopher J Silber
01/24/2000 02:54 PM

To: Grace C. Dunn/LAKE/PPRD/ABBOTT@ABBOTT, Ann P
Sullivan/LAKE/PPRD/ABBOTT@ABBOTT
cc: John M. Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Steve
Cohan/LAKE/PPRD/ABBOTT@ABBOTT, (bcc: Bruce
McCarthy/LAKE/PPRD/ABBOTT)
Subject: Analgesia Venture Monthly Highlights

Ann/Grace:

Below are the monthly highlights for the Analgesia Venture.

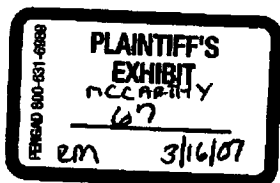
"The Go/No Go milestone was achieved on schedule. ABT-594 data presented at the October 6, 1999 Portfolio Review included Phase 2 results on the M98-833 Neuropathic Pain and M98-828 Osteoarthritis Pain studies (maximum dose 75 mcg BID). Also presented were tolerability and pharmacokinetic data from Study M99-076 (14 day BID, ascending fixed dose study). Based on the data it was decided that ABT-594 will not proceed to Phase 3, but the program will continue with the identification of maximum tolerated doses (MTD), with and without titration, of the hard gelatin capsule (HGC) dosage form, and assessment of these higher doses in Phase 2.

Study M99-076 has been completed, and the MTD of ABT-594 (without titration) is 300 mcg BID. Dosing has been completed in Study M99-120 which is an assessment of whether *titration* improves the tolerability of ABT-594 and/or allows higher doses to be tolerated. Although the data remain blinded at this time, titration appears to improve the tolerability of ABT-594. Phase 2 with doses higher than 75 mcg BID is planned to be initiated by 4/00."

Please call if you have any questions.

Chris

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ABBT0159624



McCarthy Deposition Exhibit 71

P's Exhibit CH



Tamara L. Garavalia
07/06/2000 05:02 PM

To: Aldona T Matalonis/LAKE/PPRD/ABBOTT@ABBOTT, Bruce
McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael K
Barnesen/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J
Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc: Lawrence T Caswell/LAKE/PPRD/ABBOTT@ABBOTT
Subject: M99-114 300 mcg dose group

Looks like the process of removing the high dose group(300 mcg) from M99-114 may not be so painful since we are utilizing an IVR system (Another great reason to use this system!).

The thought is (and this will be confirmed with ClinPhone hopefully tomorrow):

If ClinPhone is provided with a memo indicating what module numbers not to ship or randomize at the site - then nothing else would need to be done with the 2 NPROs that are ready for this study and clinical supplies will not be interrupted. At the end - the remaining module cartons from these 2 NPROS will be the high dose group and can be destroyed.

RQA will need to be involved with drug at the site but I think that utilizing the ClinPhone system to NOT give the site 300 mcg module carton numbers when they call in for study drug dispensing will work well. This way - no one is unblinded. The site will basically hold onto the 300 mcg module cartons and at the end of the study - they will send to D504 for destruction. Aldona has indicated that she will work with RQA on this area.

Additional supplies will be needed - approximately 25-30% more. I will review the bulk product inventory tomorrow to see how much is left. It will be much easier to blister and card new capsules instead of using from the M99-115 supplies. The M99-115 NPRO is not completed (as the study is on hold) so it is quite messy to remove drug from it. Aldona and I will work on this starting tomorrow.

Tamara



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ABBT0161395

McCarthy Deposition Exhibit 72

P's Exhibit CJ



Bruce
McCarthy /LAKE/PPRD/ABB
OTT

07/07/2000 11:13 AM

To: David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, James W
Thomas/LAKE/PPRD/ABBOTT@ABBOTT, Andrea
Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Michael K
Blamesen/LAKE/PPRD/ABBOTT@ABBOTT, Marilyn J
Collicott/LAKE/PPRD/ABBOTT@ABBOTT
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject: M99-114 Protocol Change Discussion

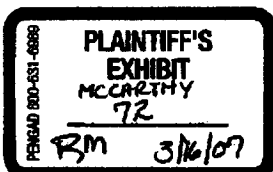
I've scheduled a meeting next week to discuss options to modify the 114 protocol. Enrollment has not met initial expectations. At the present rate of enrollment, data would not be available until June or July of 2001. We in the venture continue to work to address this situation by reasonable encouragement to sites and other modifications to the management of the study (including removal of poorly enrolling sites and replacement with back-up sites). Several protocol-related issues, however, may outweigh any encouragement or management strategies.

Of the 78 subjects enrolled to date, at least 31 have preterm. Of those, at least 20 appear to have preterm for AEs typical of our drug (nausea, vomiting and/or dizziness). Although three of these subjects dropped on day one (when they would have, at most, been exposed to 75 mcg), many of these subjects dropped in the 3-11 day time frame (the period of dose escalation resulting in 150 mcg BID at day 4, 225 mcg BID at day 6 and 300 mcg BID at day 8). Appropriately, the preterm rate has created investigator and coordinator reluctance to enroll (or, more particularly, individual sites' experience with preterms). One option to address this concern would be to remove the top dose (300 mcg BID). This doesn't address all of the issues, in that we continue to be blinded and don't know how many of these subjects that dropped out would have been randomized to 150 or 225 (assuming all events are drug related). We would, however, be responding appropriately to sites' concerns and may reduce their appropriate concerns about enrolling subjects because subjects would no longer risk randomization to the 300 mcg dose.

In addition, as with the prior study (833), there continues to be significant investigator and coordinator head-wind related to a study design that requires subjects to be off all analgesics. One option is to remove this requirement and allow subjects to enter the trial on some level of concomitant analgesia.

Please consider the ramifications of these and other possible protocol design changes in preparation for this meeting. Let's begin to discuss these possibilities for implementation in the next few weeks. The optimal enrollment time extends until 9/22/00 (in terms of date of randomization)-after that, subjects starting on drug would be in the study during the holiday season and enrollment is likely to decrease. Any changes should be incorporated into a protocol amendment to be signed off the week of 7/17 so that they can be distributed for IRB approval. That timeline might allow a majority (and I mean 50%) of sites to be able to implement the changes by mid August.

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ABBT0082516



McCarthy Deposition Exhibit 75

P's Exhibit DC



Andrea
Landsberg /LAKE/PPD/ABBO
TT
10/03/2000 07:32 AM

To: Robert J Weiland/LAKE/PPD/ABBOTT@ABBOTT
Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT,
Christopher J Silber/LAKE/PPD/ABBOTT@ABBOTT,
Bruce McCarthy/LAKE/PPD/ABBOTT@ABBOTT, George
cc: W Carter/LAKE/PPD/ABBOTT@ABBOTT, Mike
Williams/LAKE/PPD/ABBOTT@ABBOTT, James
Sullivan/LAKE/PPD/ABBOTT@ABBOTT, Larry L
Lin/LAKE/PPD/ABBOTT@ABBOTT

bcc:

Subject: ABT 594/963 Purdue meeting

Bob,

As you, Rose and I had discussed, if we move forward to set up a presentation of information to Purdue, the following people could probably do the presenting on key topics:

Predclinical ABT 594:	Jim Sullivan
Clinical ABT 594:	Bruce McCarthy
Predclinical and Clinical Plan ABT 963:	George Carter
Market Opportunity/Business Rationale:	Andrea Landsberg

If anyone has objections or would like to suggest alternate individuals, please feel free to do so.

One final comment that I neglected to bring up yesterday: George and I have had a number of conversations regarding the meaning of 'co-development' and the potential impact on development costs and timelines. I think this needs to be the topic of a separate discussion so that we can clearly define 'co-development' on our terms prior to any negotiations with a partner. Of course, Chris and the analgesia venture's input would be key in this discussion.

Andrea

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ABBT0117782



McCarthy Deposition Exhibit 77

P's Exhibit CN

ABT-594 Product Development Team Meeting

Tuesday, August 1, 2000

1:00pm - 2:30pm

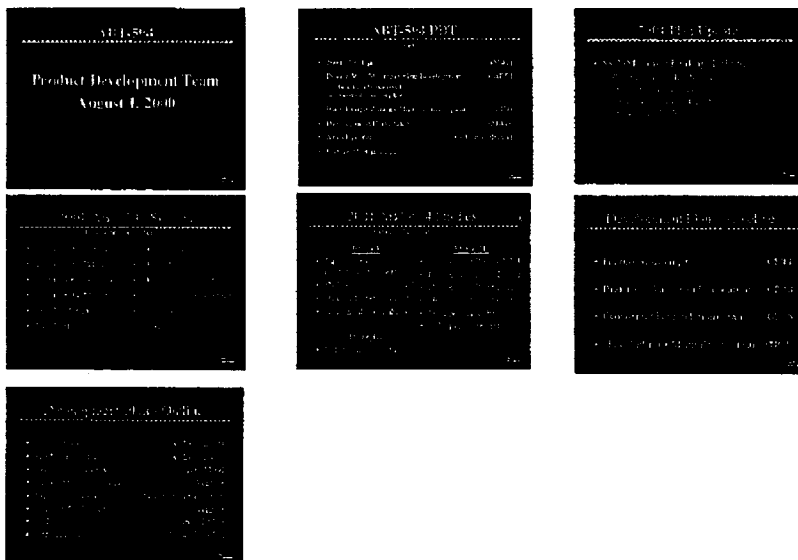
AP30-3E-Cafeteria

Minutes

Attendees:

Mike Biamesen, Bruce McCarthy, Chris Silber, Jim Ciullo, Michael Meyer, Jim Thomas, Julia Hui, Aldona Matalonis, Barbara Massa, Stan Roberts, Andrea Landsberg, Laura Robinson, Dave Stroz, Lloyd Dias, Marilyn Collicott, Teresita Curry, Dianna Ambrose, Michael Branton, Ji Zhou, Joe Machinist, Cathy Kacos.

Agenda:



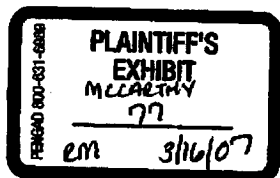
2001 Plan Update:

Currently, we have \$35 MM funded for 2001, which includes the osteoarthritis study. However, we will try to have the OA study moved to this year. This also includes Phase III studies on neuropathic pain, assuming a "Go" decision.

B:\21\000000... Product Development Team\Minutes-080100

1

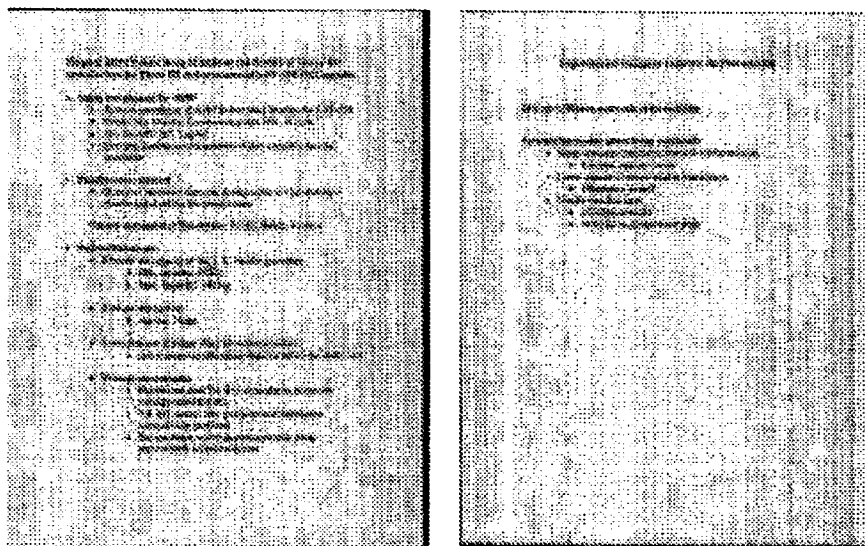
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2001 Studies:

Several Phase I, Phase II, Phase IIb and Phase III studies have been proposed for 2001. Among these are an fMRI study and Human Abuse Liability studies. The fMRI study will determine how the brain functions during pain and with pain relief on ABT-594. The fMRI study will be performed by a research group in England.

The Human Abuse Liability study will take 2 stages: 1. Pre-clinical, which will be an independent evaluation of the drug in animal models; and 2. Clinical, which will be performed by Donald Jasinski, MD at Johns Hopkins. There, Dr. Jasinski will enroll drug addicts to compare the addiction of ABT-594 to heroin and cocaine. All new, novel analgesics must go through this type of study.

PARD Update (Lloyd Dias):

The manufacturing site in Puerto Rico is the site of choice in manufacturing ABT-594 capsules. A placebo safety run has been completed. Other than a few very minor problems, the facility appears acceptable from a safety perspective. The highest drug loading will be 1500 mcg/gm.

Capital expenditures for AHPI will be minimal, however, in the long run, the facilities will need to be upgraded. Hypothetically, if AHPI had not passed standards, we do have back-

up sites that are available for manufacturing of ABT-594. However, this would cause a 6-month delay (for testing of new sites).

PARD is also working on a modified formulation to remove the microcrystalline cellulose and to lower the amount of stearic acid.

We currently have enough clinical supplies for the osteoarthritis study this year.

SPD/Analytical Update (Jim Ciullo/Dave Struz):

DTP (test and spec document for 594 drug substance) issued 7/21/00.

In June, meetings were held to discuss the mesylate route versus Mitsunobu. Both routes include recrystallization and cannot be distinguished. Gopi Menon has indicated that we must look for "remnants" of the process changes as part of the Mitsunobu route assessment. Progress has been limited due to prioritization/resource constraints.

There are NDA lots (3 Chemsyn) under test; all tests to be completed and lots approved by the end of August.

Further chemical investigation for the presence of possible detectable manufacturing impurities of Mitsunobu reaction to be finished 10/31/00. Requires assistance from SPD to synthesize chemical intermediates/reaction mixtures. Also, Mike/Aldona to call cross-functional meeting(s) to determine what is necessary to assess need for Mitsunobu runs at this time. AI Regulatory should be involved in the decision process.

Class I solvents (4 chlorinated + benzene) for the 6 lots of 2-chloro-5-hydroxypyridine and 2 clinical lots of 594 (27-335-YS-00 and 52-015-KD-00), and results to be issued by 8/11. Preliminary readout is that no Class I solvents have been found in any of the 8 samples mentioned.

If we need to make full-scale runs, we will be behind schedule and may not have enough starting materials. However, if we only do partial-scale runs, we will be on schedule with existing starting materials. We will actually plan for 3 full-scale runs for 2001 to determine if the budget can hold that. This will cost approximately \$1MM, including head count.

Development Plan (Mike Biarnesen):

We will be sending out sections to certain individuals for their input to the Development Plan. The projected date of completion for the Development Plan is the end of August, 2000. A meeting will need to take place to determine bridging studies in Japan.

Other Updates:

Marilyn Collicott provided an update on the M99-114 (Neuropathic Pain) study. Currently we have 99 subjects randomized with an approximate 50% screen failure rate. Our goal of enrollment is 320 subjects. There has been much concern with the drop out rate. Therefore, we have sent out surveys to each site to determine "who" and "why" subjects are dropping out.

Julia Hui provided an update on the rat carcinogenicity study. We are close to maximum drop out (21 rats). After the study has ended, it will take the pathologist approximately 6 months for evaluations and the report will be ready after that. The FDA has accepted our proposal for managing the drop-out rate. Julia also mentioned that the antigeucity studies will be required for Japan.

Andrea Landsberg updated the name selection for ABT-594. There were several names approved by the Trademark committee. Among these are Numira, Nufora, and Amarquil [check spelling]. Our goal is to have 10 names to bring to market research.

Lloyd Dias mentioned that we will need to start thinking about capsule color. A separate meeting will be scheduled.

Mike Meyer is still looking into back-up compounds for ABT-594. Compound 312046 is similar, along with a few other compounds.

Mike Biarnesen mentioned that, in the future, we may combine the Product Development Team meetings with the Clinical Trial Team meetings to form one monthly meeting.

A separate meeting will be scheduled to discuss the registration requirements for Japan with Nigel Livesey, Laura Robinson, Carol Meyer, Bruce McCarthy, Mike Biarnesen, and Cary Buschen-Schmidt.

McCarthy Deposition Exhibit 82

P's Exhibit DE



Mike
Williams /LAKE/PPRD/ABBO
TT

10/12/2000 03:01 PM

To Jennifer Smoter/LAKE/PPD/ABBOTT@ABBOTT
cc Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject Re: NNR documents

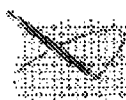
Jennifer: I think Mike Decker has addressed some of the document issues. Another real issue we must address given some of the internal discussions around the clinical trials on ABT-594 is whether we want to make any statements in the next few weeks until a decision is made by Jeff Leiden as to whether we continue the trials.

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ABBT0118072

Pl Exhibit 82 3/16/07 R.M.

McCarthy Deposition Exhibit 84

P's Exhibit DM



James
Sullivan/LAKE/PPRD/ABBO
TT

11/02/2000 04:04 PM

To: Robert J Weiland/LAKE/PPD/ABBOTT@ABBOTT
Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT,
Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Mike
Williams/LAKE/PPRD/ABBOTT@ABBOTT, Andrea
cc: Landsberg/LAKE/PPD/ABBOTT@ABBOTT, Larry L
Lin/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K
Waleska/LAKE/PPD/ABBOTT@ABBOTT

bcc

Subject: Re: Pharmacia meeting

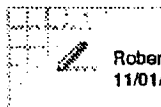
Bob,

I do not want to make things confusing but I was under the strong impression after the meeting with Dan and John a couple of weeks ago that we were to limit the discussion to ABT-594 only at this time and no discussion of other compounds advanced to clinical status or the preclinical project in general was to be revealed. Dan re-iterated to this to me on his way out of the meeting. Hence, I would suggest that the agenda etc should be limited to

- Predclinical profile of ABT-594 (15-20mins)
- Clinical Profile of ABT-594 (Bulk of time)
- Brief description of the type of collaboration we have in mind.

Thanks
Jim

Robert J Weiland



Robert J Weiland
11/01/2000 16:15

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT
cc: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Mike Williams/LAKE/PPRD/ABBOTT@ABBOTT,
Andrea Landsberg/LAKE/PPD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT,
Larry L Lin/LAKE/PPD/ABBOTT@ABBOTT, Rosemarie K Waleska/LAKE/PPD/ABBOTT@ABBOTT
Subject: Re: Pharmacia meeting

Bruce:

Thank you for your message. Unfortunately with everyone's travel calendar, a pre-planning meeting has not been very feasible.

The primary purpose for this meeting is to share data with Pharmacia that might encourage them to partner with us on this project. Although time has elapsed, Steve A. is aware of this from his days at Abbott, although he may not be fully facile with the most recent data.

At the end of the day, there is no other way I am aware of to broach a partnership without disclosure of the technical and scientific information. Hence, unless there is something particular that we should hold back in this first round, then we need to provide the info. One area where I have a concern is the nausea and vomiting issue. If anyone has a suggestion on how we can handle that without frightening our partner, it would be very well received.

In terms of the meeting, we should be prepared to share with them

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- I - Discussion of the existing data / program
- II - Plans for moving the project ahead
- III - Other compounds that have been moved ahead
- IV - Brief description of the type of collaboration we have in mind

The first three should be handled by the Technical Team. The latter by Larry Lin. I apologize, in advance, that I will be out of the country and unable to attend next Tuesday.

Should you have ideas for a better agenda. Please get back to me quickly as I would like to finalize with Dick Welter at Pharmacia.

Best Regards,

Bob

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ABBT0120837

McCarthy Deposition Exhibit 91

P's Exhibit DZ



James W
Thomas/LAKE/PPRD/ABBO
TT

12/21/2000 08:46 AM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject: Re: n/v rate [E]

Yes you are correct on the first case, just sum the N (or n) across the treatments to get the overall rates.

Number 2, just between you and me (and Sue Nunn)....

you need to go in through REFLECTION X and on the bottom there is a icon that looks like a pair of glasses (not the drinking type), double click on the icon and the then clinical browser comes up with instructions to enter study number and then the 594 password (I think the password is the whole A number [165594], but I've been wrong in the past). Now, I have never ever used this so I could be wrong.

Jim

Bruce McCarthy 12/21/2000 08:31 AM

Bruce McCarthy 12/21/2000 08:31 AM

To: James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Re: n/v rate [E]

Thanks! I assume to get the AE rates for the entire blinded population, I add up the N's in the columns. Thus, the total N in the database below is 129 and there are a total of 25 Nausea's (19%) and 10 Vomiting's (7.8%) and 9 Ladies dancing. Is this correct?

Also...please keep this next question to yourself as the last time I asked, Rich Manski apparantly nearly had a stroke. There's a way now for us knuckleheads in the venture to access the current database I don't remember how I do this (on my desktop or workstation?) or what my password was. I think if you know the name of the system, I can probably go a long way in reconstructing how to get onto this system
JAMES W THOMAS

JAMES W THOMAS

12/21/2000 06:53 AM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Re: n/v rate [E]

Bruce,

If you are asking about current 114 N/V rates, I have included a current blinded (all real data) AE table for the 114 study. If you are talking about something else, please feel free to expound.

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ABBT0080180

P1. Exhibit 91 3/16/07 RM

21DEC2000 06:34 <! 114aes.sas thomasj >
 ABT-594 (ABBOTT-165594)
 STUDY M99-114
 R&D/XX/XXX - CLINICAL/STATISTICAL
 TABLE PAGE 1

ALL TREATMENT EMERGENT ADVERSE EVENTS DURING THE TREATMENT PERIOD
 GROUPED BY BODY SYSTEM AND COSTART TERM
 (ALL RANDOMIZED SUBJECTS)

	XXXXXXX (N=21)	ABT-594 XXX MCG (N=42) (A)	ABT-594 XXX MCG (N=36) (B)	ABT-594 XXX MCG (N=30) (C)	P-VALUE 9
BODY SYSTEM/COSTART TERM	n (%)	n (%)	n (%)	n (%)	
TOTAL SUBJECTS WITH ANY EVENT	18 (86%)	35 (83%)	28 (78%)	27 (90%)	
BODY AS A WHOLE					
ABDOMEN ENLARGED	0	0	0	1 (3%)	
ABDOMINAL PAIN	1 (5%)	0	0	0	
ACCIDENTAL INJURY	0	1 (2%)	1 (3%)	1 (3%)	
ASTHENIA	1 (5%)	1 (2%)	3 (8%)	6 (20%)	
BACK PAIN	1 (5%)	0	2 (6%)	0	
CHEST PAIN	0	2 (5%)	1 (3%)	0	
CYST	0	0	0	1 (3%)	
HEADACHE	3 (14%)	4 (10%)	3 (8%)	2 (7%)	
INFECTION	1 (5%)	2 (5%)	4 (11%)	1 (3%)	
INFECTION FUNGAL	0	0	1 (3%)	0	
MALADISE	0	0	0	1 (3%)	
PAIN	0	1 (2%)	4 (11%)	2 (7%)	
PELVIC PAIN	0	1 (2%)	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	6 (29%)	8 (19%)	13 (36%)	9 (30%)	
CARDIOVASCULAR SYSTEM					
ANGINA PECTORIS	0	0	0	1 (3%)	
CARDIOVASCULAR DISORDER	0	0	0	1 (3%)	
ELECTROCARDIOGRAM ABNORMAL	0	0	0	1 (3%)	
HYPERTENSION	0	1 (2%)	2 (6%)	0	
HYPOTENSION	1 (5%)	0	0	0	
PALPITATION	0	0	2 (6%)	0	
SYNCOPE	0	0	0	1 (3%)	
VASODILATATION	0	1 (2%)	2 (6%)	0	
SUBJECTS WITH ONE OR MORE EVENTS	1 (5%)	2 (5%)	5 (14%)	4 (13%)	

NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE COSTART TERMS SHOULD BE GREATER THAN OR EQU
 SYSTEM TOTAL. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT COSTART TERMS WHICH ARE IN THE SAME BODY SYSTE
 IS COUNTED ONLY ONCE IN THE BODY SYSTEM TOTAL.

\$ P-VALUE FOR PAIRWISE COMPARISONS BETWEEN PLACEBO AND INDICATED TREATMENT GROUP USING FISHER'S EXACT TEST.

Program Source Code: /thomasj/ABT-594/M99-114/A/SAFETY/AE/114aes.sas

21DEC2000 06:34 <! 114aes.sas thomasj >
 ABT-594 (ABBOTT-165594)
 STUDY M99-114
 R&D/XX/XXX - CLINICAL/STATISTICAL
 TABLE PAGE 2

ALL TREATMENT EMERGENT ADVERSE EVENTS DURING THE TREATMENT PERIOD
 GROUPED BY BODY SYSTEM AND COSTART TERM
 (ALL RANDOMIZED SUBJECTS)

XXXXXXX (N=21)	ABT-594 XXX MCG (N=42)	ABT-594 XXX MCG (N=36)	ABT-594 XXX MCG (N=30)
-------------------	------------------------------	------------------------------	------------------------------

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 ABBT0080181

BODY SYSTEM/COSTART TERM	(A)		(B)		(C)		P-VALUE \$
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
DIGESTIVE SYSTEM							
ANOREXIA	0	1 (2%)	0		1 (3%)		
CHOLECYSTITIS	0	1 (2%)	0		0		
CONSTIPATION	0	1 (2%)	0		1 (3%)		
DIARRHEA	1 (5%)	2 (5%)	1 (3%)		2 (7%)		
DRY MOUTH	0	1 (2%)	0		0		
DYSPEPSIA	1 (5%)	2 (5%)	0		2 (7%)		
ERUCTION	1 (5%)	0	0		1 (3%)		
FLATULENCE	1 (5%)	1 (2%)	0		1 (3%)		
GASTRITIS	0	1 (2%)	0		0		
GASTROENTERITIS	0	2 (5%)	0		0		
GASTROINTESTINAL DISORDER	0	1 (2%)	0		0		
GLOSSITIS	1 (5%)	0	0		0		
MELENA	0	1 (2%)	0		0		
NAUSEA	5 (24%)	8 (19%)	6 (17%)		6 (20%)		
STOMATITIS	1 (5%)	0	0		0		
THIRST	0	0	0		1 (3%)		
TOOTH DISORDER	1 (5%)	0	0		0		
VOMITING	1 (5%)	2 (5%)	2 (6%)		5 (17%)		
SUBJECTS WITH ONE OR MORE EVENTS	6 (29%)	14 (33%)	7 (19%)		9 (30%)		
HEMIC AND LYMPHATIC SYSTEM							
ECCHYMOSIS	0	1 (2%)	0		0		
SUBJECTS WITH ONE OR MORE EVENTS	0	1 (2%)	0		0		

NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE COSTART TERMS SHOULD BE GREATER THAN OR EQUAL TO THE TOTAL NUMBER OF SUBJECTS. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT COSTART TERMS WHICH ARE IN THE SAME BODY SYSTEM IS COUNTED ONLY ONCE IN THE BODY SYSTEM TOTAL.

\$ P-VALUE FOR PAIRWISE COMPARISONS BETWEEN PLACEBO AND INDICATED TREATMENT GROUP USING FISHER'S EXACT TEST.

Program Source Code: /thomasj/ABT-594/M99-114/A/SAFETY/AB/114aes.sas

21DEC2000 06:34 < 114aes.sas thomasj >
 ABT-594 (ABBOT-165594)
 STUDY M99-114
 R4d/XX/XXX - CLINICAL/STATISTICAL
 TABLE PAGE 3

ALL TREATMENT EMERGENT ADVERSE EVENTS DURING THE TREATMENT PERIOD
 GROUPED BY BODY SYSTEM AND COSTART TERM
 (ALL RANDOMIZED SUBJECTS)

BODY SYSTEM/COSTART TERM	XXXXXXX (N=21)	ABT-594 XXX MCG (N=42) (A)	ABT-594 XXX MCG (N=36) (B)	ABT-594 XXX MCG (N=30) (C)	P-VALUE \$
	n (%)	n (%)	n (%)	n (%)	
METABOLIC AND NUTRITIONAL DISORDERS					
DEHYDRATION	0	1 (2%)	0	0	
EDEMA	0	0	1 (3%)	0	
HYPERCALCEMIA	0	1 (2%)	0	0	
HYPOGLYCEMIA	0	0	1 (3%)	0	
KETOSIS	0	1 (2%)	0	0	
PERIPHERAL EDEMA	0	1 (2%)	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	0	3 (7%)	2 (6%)	0	
MUSCULOSKELETAL SYSTEM					
ARTHRALGIA	0	1 (2%)	0	0	
MYALGIA	0	0	0	1 (3%)	
SUBJECTS WITH ONE OR MORE EVENTS	0	1 (2%)	0	1 (3%)	

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 ABBT0080182

NERVOUS SYSTEM				
ABNORMAL DREAMS	1 (5%)	5 (12%)	3 (6%)	3 (12%)
ABNORMAL GAIT	1 (5%)	0	0	0
ANXIETY	0	2 (5%)	0	0
CONFUSION	1 (5%)	0	0	0
DIZZINESS	4 (19%)	8 (19%)	4 (11%)	5 (17%)
INSOMNIA	0	2 (5%)	1 (3%)	0
NERVOUSNESS	0	0	2 (6%)	0
NEUROPATHY	0	1 (2%)	0	1 (3%)
PARESTHESIA	1 (5%)	0	0	0
REFLEXES DECREASED	0	0	0	1 (3%)
THINKING ABNORMAL	1 (5%)	1 (2%)	0	0
TREMOR	0	0	1 (3%)	1 (3%)
SUBJECTS WITH ONE OR MORE EVENTS	5 (24%)	15 (36%)	9 (25%)	8 (27%)

NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE COSTART TERMS SHOULD BE GREATER THAN OR EQUAL TO THE TOTAL NUMBER OF SUBJECTS. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT COSTART TERMS WHICH ARE IN THE SAME BODY SYSTEM IS COUNTED ONLY ONCE IN THE BODY SYSTEM TOTAL.

\$ P-VALUE FOR PAIRWISE COMPARISONS BETWEEN PLACEBO AND INDICATED TREATMENT GROUP USING FISHER'S EXACT TEST.

Program Source Code: /thomasj/ABI-594/M99-114/A/SAFETY/AE/114aes.sas

21DEC2000 06:34 <1 114aes.sas thomasj >
 ABT-594 (ABBOTT-165594)
 STUDY M99-114
 R&D/XX/XXX - CLINICAL/STATISTICAL
 TABLE PAGE 4 - LAST TABLE PAGE

ALL TREATMENT EMERGENT ADVERSE EVENTS DURING THE TREATMENT PERIOD
 GROUPED BY BODY SYSTEM AND COSTART TERM
 (ALL RANDOMIZED SUBJECTS)

	XXXXXXX (N=21)	ABI-594 XXX MCG (N=42) (A)	ABI-594 XXX MCG (N=36) (B)	ABI-594 XXX MCG (N=30) (C)	P-VALUE \$
BODY SYSTEM/COSTART TERM	n (%)	n (%)	n (%)	n (%)	
RESPIRATORY SYSTEM					
DYSPNEA	0	0	2 (6%)	0	
EPISTAXIS	0	1 (2%)	0	0	
RHINITIS	1 (5%)	0	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	1 (5%)	1 (2%)	2 (6%)	0	
SKIN AND APPENDAGES					
ECZEMA	1 (5%)	0	0	0	
RASH	0	1 (2%)	0	0	
SKIN DISCOLORATION	0	1 (2%)	0	0	
SKIN DISORDER	0	1 (2%)	0	0	
SWEATING	0	3 (7%)	0	0	
URTICARIA	0	1 (2%)	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	1 (5%)	7 (17%)	0	0	
SPECIAL SENSES					
ABNORMAL VISION	0	0	1 (3%)	1 (3%)	
AMBLYOPIA	0	0	1 (3%)	2 (7%)	
CONJUNCTIVITIS	0	0	0	1 (3%)	
TASTE PERVERSION	1 (5%)	1 (2%)	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	1 (5%)	1 (2%)	2 (6%)	4 (13%)	
UROGENITAL SYSTEM					
ABNORMAL EJACULATION	0	1 (2%)	0	0	
URINATION IMPAIRED	0	0	0	1 (3%)	
URINE ABNORMALITY	1 (5%)	1 (2%)	0	0	
SUBJECTS WITH ONE OR MORE EVENTS	1 (5%)	2 (5%)	0	1 (3%)	

NOTE: THE SUM OF THE TOTAL NUMBER OF SUBJECTS REPORTING EACH OF THE COSTART TERMS SHOULD BE GREATER THAN OR EQUAL TO THE TOTAL NUMBER OF SUBJECTS.

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SYSTEM TOTAL. A SUBJECT WHO REPORTS TWO OR MORE DIFFERENT COSTART TERMS WHICH ARE IN THE SAME BODY SYSTEM IS COUNTED ONLY ONCE IN THE BODY SYSTEM TOTAL .
\$ P-VALUE FOR PAIRWISE COMPARISONS BETWEEN PLACEBO AND INDICATED TREATMENT GROUP USING FISHER'S EXACT TEST .

Program Source Code: /thomasj/ABT-594/M99-114/A/SAFETY/AE/114aes.sas

Bruce McCarthy 12/20/2000 03:30 PM

Bruce McCarthy 12/20/2000 03:30 PM

To: James W Thomas/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: n/v rate

Jim-For the IND update you had a blinded AE rate. Do you know what the current rates are for nausea and vomiting (what is the N and do these rates include the fake data??

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McCarthy Deposition Exhibit 92

P's Exhibit EA



Bruce
McCarthy /LAKE/PPRD/ABB
OTT

12/21/2000 09:29 AM

To: Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject: landsberg email

andrea, as part of the portfolio process from the other day, asked that I give her an update on the nausea and vomiting story. Yesterday I sent her the 833/826 rates. Here's what I sent her on 114.

----- Forwarded by Bruce McCarthy/LAKE/PPRD/ABBOTT on 12/21/2000 09:28 AM -----

Bruce McCarthy 12/21/2000 09:27 AM

To: Andrea Landsberg/LAKE/PPD/ABBOTT@ABBOTT
cc:
Subject: n/v

Here's the info for 114

REMEMBER...

THIS IS BLINDED

That means the rates include data for all groups combined (so, probably very low nausea and vomiting in placebo and higher rates in the 300 mcg BID group)

THE DATABASE IS NOT CLEAN

Data are first pass and have not completed the query process

THIS IS THE ONE AND ONLY TITRATION SCHEME WE'VE TESTED

There will be commercially very viable titration schemes other than this one that will result in lower AE rates

THIS IS NOT THE RATE OF NAUSEA AND VOMITING FOR ABT-594 AT LAUNCH

Is a tree in the forest the same as an authentic Chippendale chest of drawers? If you would spend \$5 for some wood at home depot, why would you spend \$10,000 for the chest of drawers? Because they're not the same. Similarly, why would you value the final product of ABT-594 while it's still in the lumber stage?

The database has 129 patients currently (261 randomized, but only 129 patients' data is in).

Nausea: 19%
Vomiting: 7.8%

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P1. Exhibit 92 3/16/07 RM

McCarthy Deposition Exhibit 93

P's Exhibit EC



Bruce
McCarthy /LAKE/PPRD/ABB
OTT

12/21/2000 10:24 AM

To Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT
cc
bcc
Subject Purdue presentation



ABT594Purdue12100.ppt

CONFIDENTIAL
ABBT0118174

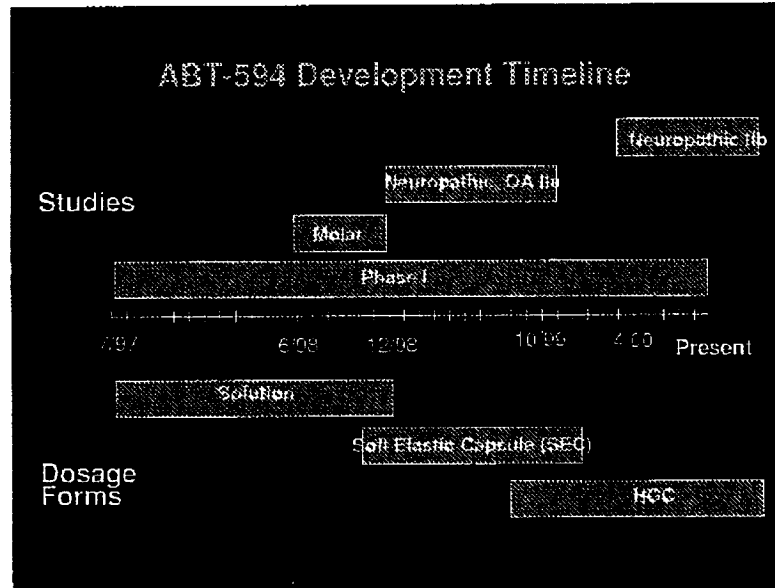
P1. Exhibit 93 3/16/07 RM

ABT-594's analgesic potential demonstrated
in:

Molar Extraction

Neuropathic Pain

Osteoarthritis



ABT-594 Overview

- Pharmacokinetics
- Development strategy
- Phase IIa results
 - Dental, osteoarthritis, and neuropathic pain
 - Context: currently available analgesics
- Phase IIb status

ABT-594

Pharmacokinetics

- Half-life ($t_{1/2}$): about 8-12 hours
- Dose proportional
- AUC, C_{max} similar across formulations (solution, SEC, HGC)
- AUC, C_{max} similar with/without food
- T_{max} varies with formulation, food
- No clinically significant effects on cytochrome P450 isoforms
- Elimination primarily through renal excretion, about

Strategy

What characterizes an innovative analgesic?

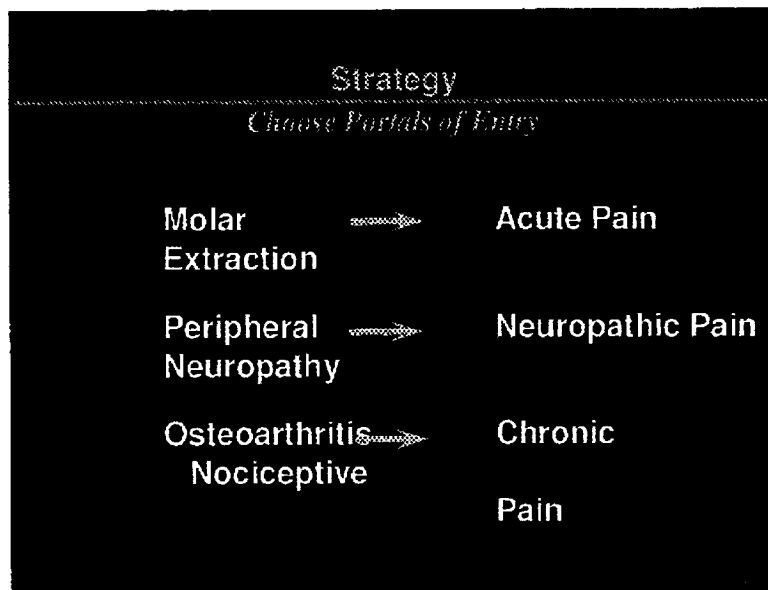
Spectrum of activity

Time of onset/duration

Level of efficacy

Safety/efficacy ratio

Strategy		
<i>Spectrum of Activity: Where to Start?</i>		
<u>Acute</u>	<u>Neuropathic</u>	<u>Chronic Nociceptive</u>
Post-dental surgery	Diabetic polyneuropathy	Cervicalgia
Spains and strains	Idiopathic polyneuropathy	Chronic back pain
Acute back pain	Alcohol polyneuropathy	Rheumatoid arthritis
Trauma	Drug-induced	Cancer pain
Post-general surgery	polyneuropathy	Fibromyalgia
Post-orthopedic surgery	HIV predominantly sensory neuropathy	Sickle cell disease
Dysmenorrhea	Back pain	EMG disorder
Renal colic	Cancer pain	Burns
Biliary colic	Trigeminal neuralgia	Tennis elbow
Furunculitis	Postherpetic neuralgia	Chronic visceral pain
Infections	Thalamic pain syndrome	
	Spinal cord injury	
	Multiple sclerosis	
	Complex regional pain syndromes (I, II)	
	Atypical facial pain	



ABT-594

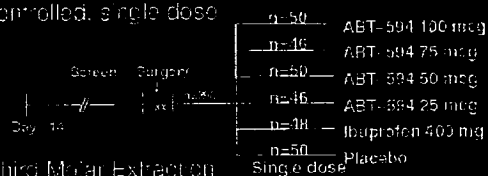
Phase IIa Results

- * Efficacy Results
 - Molar Extraction
 - Neuropathic Pain
 - Osteoarthritis Pain

Molar Extraction Study

Design

- 200 patients, randomized, double blind, placebo-controlled, single dose



- Third Molar Extraction

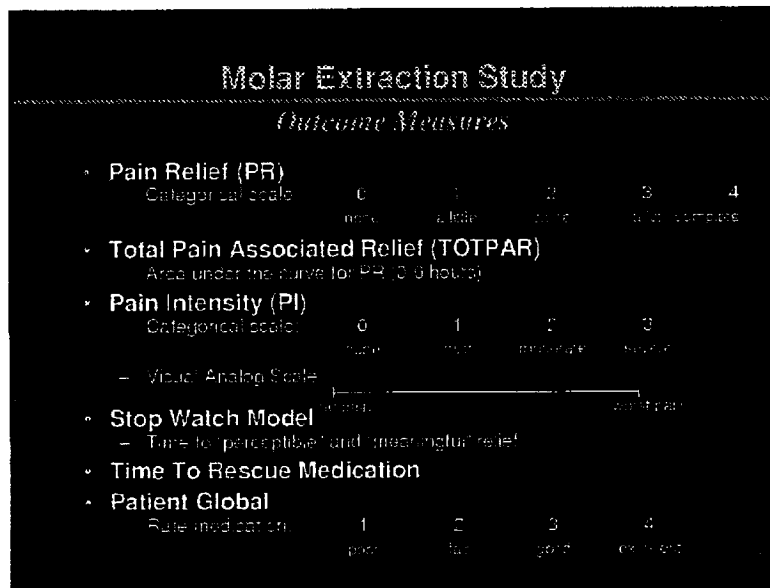
- Outcome Measures:

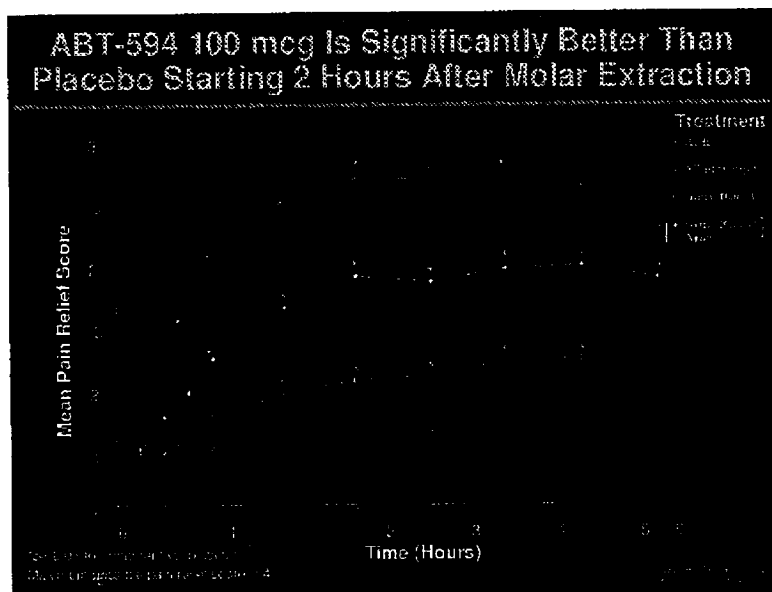
Pain Relief (PR)

Categorical scale

0 1 2 3 4
none mild moderate severe

- Power: 70% to detect 47% difference
- Solution

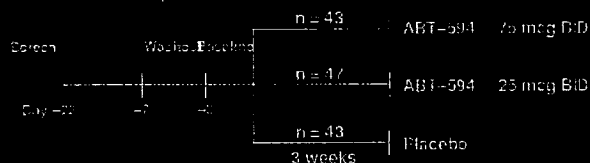




Neuropathic Pain Pilot

Design

- 138 patients, randomized, double-blind, placebo-controlled, multiple dose



- Distal Symmetric Polyneuropathy
 - 52% idiopathic
 - 46% Diabetic
- Power: 56% to detect 20% of difference
- Soft Elastic Capsule

Neuropathic Pain Pilot

Outcome Measures

- Pain Intensity (PI)
 - Categorical Scale:

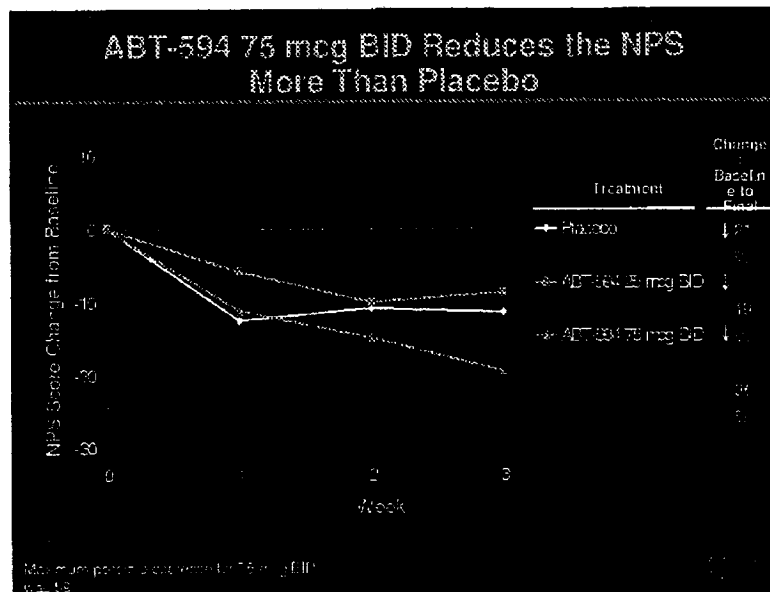
0	1	2
none	mod	moderate/sever

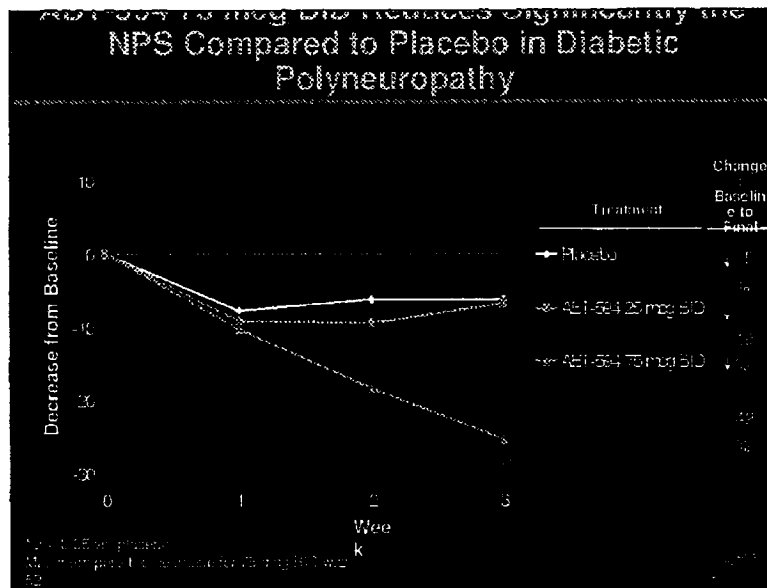
- Visual Analog Scale (0-100 mm) possible

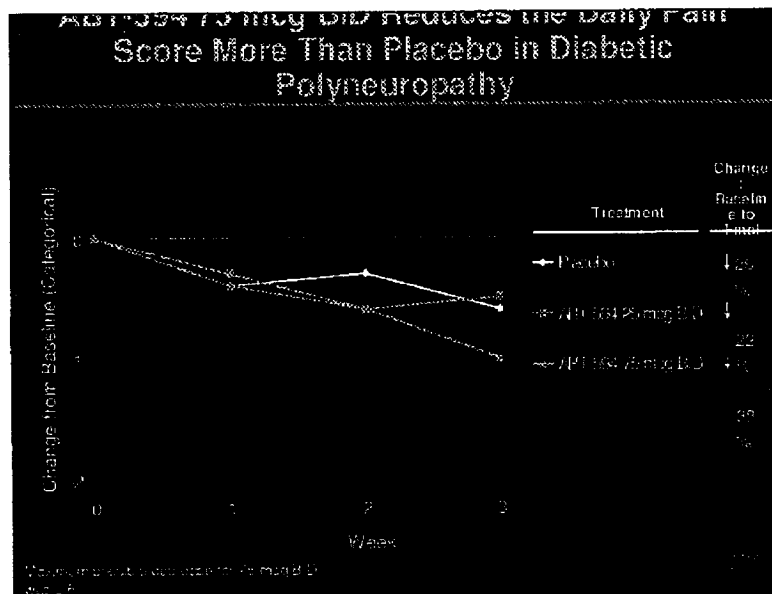
no pain worst

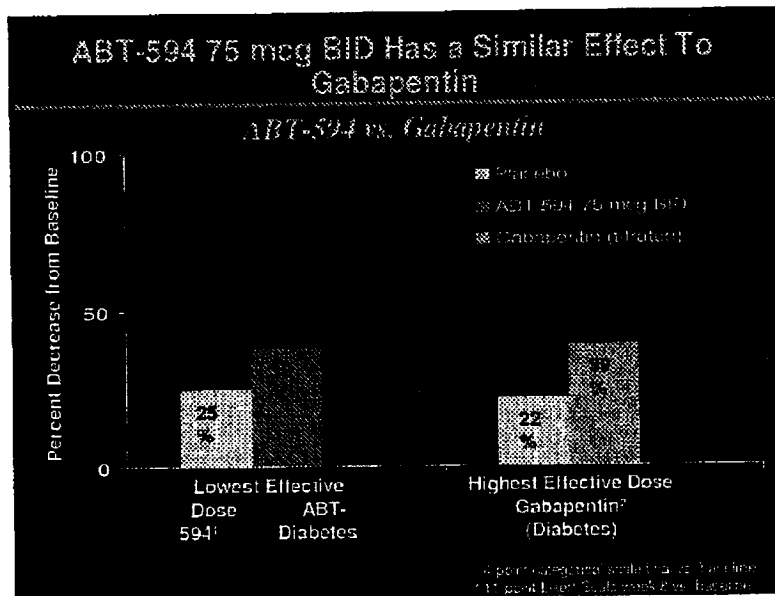
- Neuropathic Pain Scale (NPS)
 - 10 items (e.g., sharp, hot, intense), for total 0-100 points

Please use the scales below to tell us how sharp your pain is. The most sharp used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."





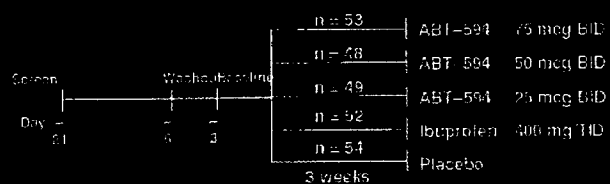




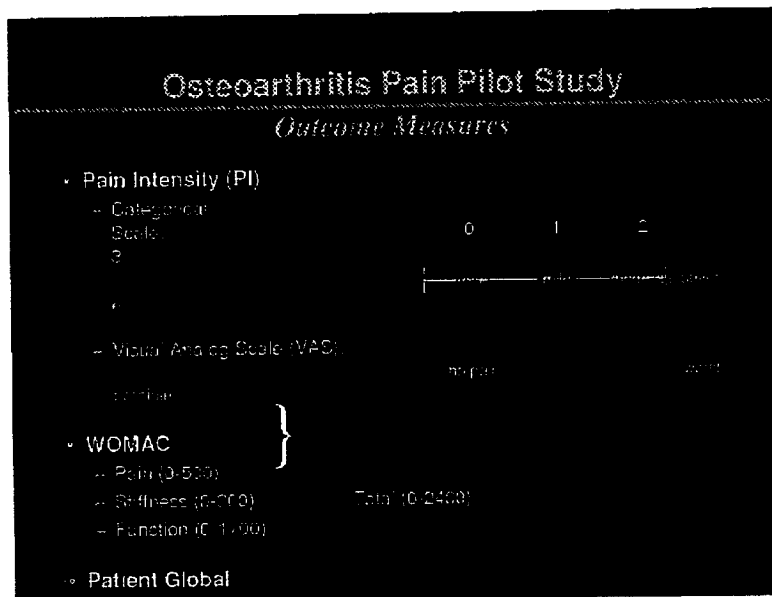
Osteoarthritis Pain Pilot

Design

- 256 patients, randomized, double-blind, placebo-controlled



- Power: 56% to detect 20% of difference
- Soft Elastic Capsule



Osteoarthritis Pain Pilot Study

WOMAC

Pain How much pain do you have...

 - Walking on a flat surface?

 - Going up or down stairs

 none |-----| severe

Stiffness How severe is your stiffness...

 - After sitting, lying, or resting later in the day?

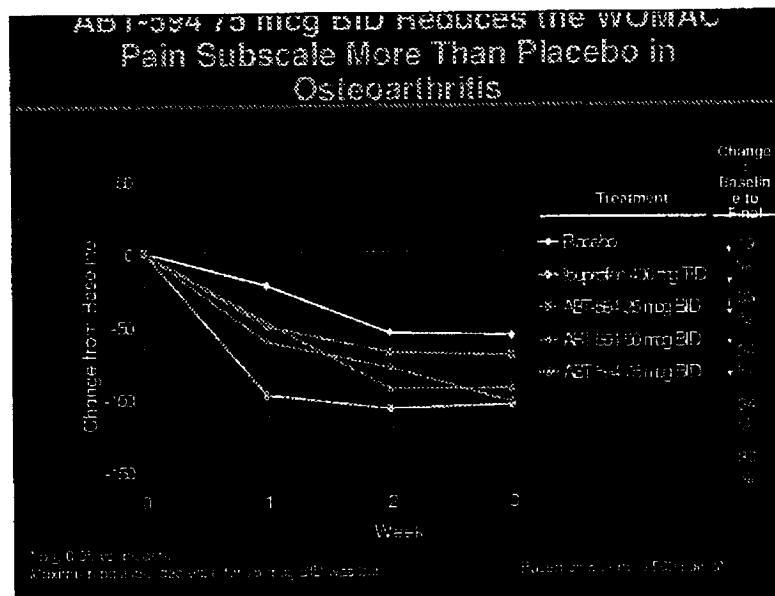
 no stiffness |-----| extreme stiffness

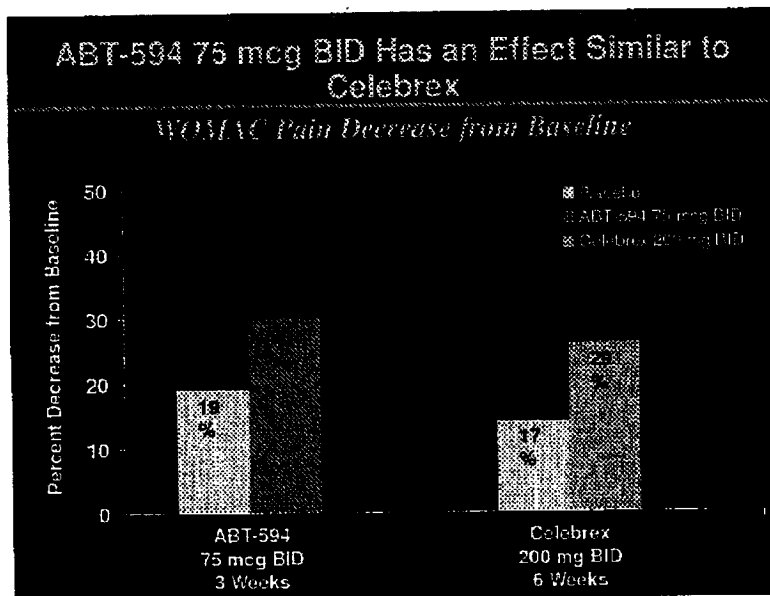
Function What degree of difficulty do you have...

 - Descending stairs?

 - Rising from bed?

 no difficulty |-----| extreme difficulty





ABT-594

Phase IIa Efficacy Conclusions

- Analgesic Potential Demonstrated

- Molar Extraction

- Significance vs. placebo starting at 2 hours

- Neuropathic Pain

- 75 mg BID may be lowest effective dose for patients with painful diabetic polyneuropathy

- Osteoarthritis Pain

- 75 mg BID may be lowest effective dose as judged by WOMAC scores

Adverse Event Rates for Select Analgesics

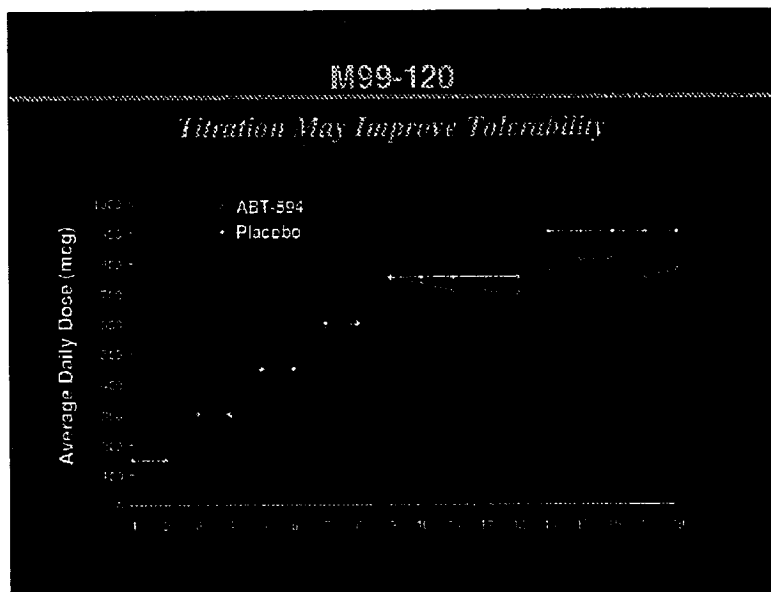
	Gabapentin	Ultram ¹	OxyContin ²	ABT-
594				
Event	3600 mg d	50-100 mg q4-6 hr		75
mg BID				
Confusion	8 %	NA	NA	0 %
Somnolence	23 %	NA	23 %	0 %
Dizziness	24 %	37 %	13 %	7 %
Nausea	8 %	36 %	23 %	5 %
Vomiting	1 %	13 %	12 %	5 %
Constipation	NA	38 %	23 %	1 %
¹ Constipation not reported with Ultram ¹ in this study.				
² Constipation not reported with OxyContin ² in this study.				
NA: Not available				

M99-076 & M99-120

Titration may improve tolerability

	M99-076 300 mcg BID (no titration) n (%)	M99-120 (titration) n (%)
Day	1-8 n=9	1-8 ^a n=15
Nausea	5 (56)	5 (33)
Vomiting	4 (44)	3 (20)
Dizziness	6 (67)	10 (67)

^a Day 1 to 4 mcg BID; Day 5 to 8 mcg BID; Day 9 to 12 mcg BID; Day 13 to 16 mcg BID; Day 17 to 20 mcg BID



ABT-594

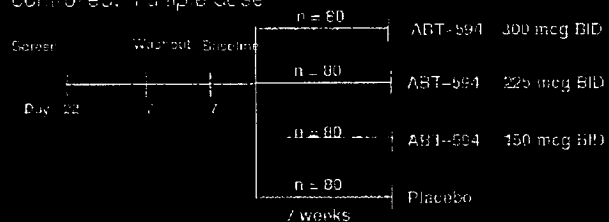
Phase IIa Conclusions

- Analgesic potential demonstrated
- Phase IIa studies included inadequate dose ranging
 - SLC tolerated better than predicted by solution
 - HCC tolerated in limited Phase I population to 300 mg BID fed
- Full analgesic potential will be defined with adequate dose ranging studies in Phase IIb

M99-114: Neuropathic Pain

Design

- 320 patients, randomized, double blind, placebo-controlled, multiple dose



- Diabetic Distal Symmetric Polyneuropathy
- 7-Day Primer Phase, Treatment Visits at 2, 3, 5 and 7 weeks
- Power: 88% with 0.05 Type I to detect 39% ABT-594 improvement, 25% placebo (ES 0.46)

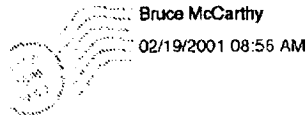
M09-114: Neuropathic Pain

Outcome Measures

- Primary
 - Weekly average of daily pain (11 point Likert in a diary)
- Secondary
 - Site-based pain scale (11 point Likert)
 - Neuropathic Pain Scale
 - Patients' Global Impression of Change
 - Physicians' Global Impression of Change
 - SF-36

McCarthy Deposition Exhibit 103

P's Exhibit EP



Bruce McCarthy

02/19/2001 08:56 AM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT@ABBOTT, Michael K Blanesen/LAKE/PPRD/ABBOTT@ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT@ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Kennan C Marsh/LAKE/PPRD/ABBOTT@ABBOTT, Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, David D Morris/LAKE/PPRD/ABBOTT@ABBOTT, Howard S Cheskin/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Scientific Strategy for ABT-594/NNR Tolerability

Please note the Scientific Strategy for ABT-594/NNR Tolerability Meeting to take place tomorrow. This meeting is a follow-on to the Leiden review, in which a recommendation was heard for a comprehensive strategy to address tolerability issues related to NNRs for pain, including ABT-594 and follow-ons. The meeting is intended to initiate a process of planning and execution to improve tolerability via all available avenues, including (but not limited to): generation of more selective follow-on compounds, follow-on compounds with different pharmacokinetics, pharmaceutical and/or dosing manipulation of ABT-594, etc. Any strategies to improve the tolerability of NNRs for pain would be directed by a scientific basis for the tolerability concerns.

This first meeting is intended to brainstorm how we might approach this issue. We should begin to define issues, scope, vision, potential plans of action, etc. In the near future, we should clarify our strategy and document it. In addition, we'll need to develop a timeline for execution.

Please come prepared with your ideas on tolerability issues. I have attached an agenda.

See you tomorrow!

Bruce.



Tolerability21901.doc

----- Forwarded by Bruce McCarthy/LAKE/PPRD/ABBOTT on 02/19/2001 08:41 AM -----

Calendar Entry

☐ Appointment ☒ Invitation ☐ Event ☐ Reminder ☐ Anniversary

Brief description:

Scientific Strategy for ABT-594/NNR Tolerability - Analgesia Venture Conf Room - w/Lunch

Date:

02/20/2001

Time:

11:00 AM - 12:30 PM

Detailed description:

Invitations have been sent to: Bruce McCarthy/LAKE/PPRD/ABBOTT, Christopher J Silber/LAKE/PPRD/ABBOTT, Michael K Blanesen/LAKE/PPRD/ABBOTT, James Sullivan/LAKE/PPRD/ABBOTT, Michael D Meyer/LAKE/PPRD/ABBOTT, Walid Awni/LAKE/PPRD/ABBOTT, Richard G Granneman/LAKE/PPRD/ABBOTT, Kennan C Marsh/LAKE/PPRD/ABBOTT, Marleen H Verlinden/LAKE/PPRD/ABBOTT, David D Morris/LAKE/PPRD/ABBOTT, Howard S Cheskin/LAKE/PPRD/ABBOTT

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.....
Chairperson: Nancy M. Peltz, AKE PPR/ABBOTT
This meeting repeats starting on (if the date occurs on a weekend the meeting).

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ABT-594 Tolerability Brainstorm Discussion
Agenda
February 19, 2001

- 1 Brief Review of Tolerability Issues to date
- 2 Individual perspectives on issues and questions related improving tolerability
Sullivan/Meyer/Marsh

Awni/Granneman

Cheskin

Morris

McCarthy
- 2 Begin to define scope and vision, prioritize issues and questions and identify prerequisites
- 3 Define Next Steps, including potential processes (e.g. analyses, discussions, consultations, trials, etc) to solve/answer prioritized issues and questions

[FILENAME]

Created on 2/19/2001 8:34:00 AM

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McCarthy Deposition Exhibit 107

P's Exhibit 21

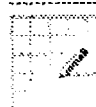


Christopher J
Silber/LAKE/PPRD/ABBOTT
03/06/2001 03:27 PM

To Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Michael
K Blamesen/LAKE/PPRD/ABBOTT@ABBOTT
cc James Sullivan/LAKE/PPRD/ABBOTT@ABBOTT, Richard J
Marasco/LAKE/PPD/ABBOTT@ABBOTT
bcc
Subject Re: ABT-594 - Purdue Response

attached, fyl

Forwarded by Christopher J Silber/LAKE/PPRD/ABBOTT on 03/06/2001 03:25 PM



Robert J Weiland
03/06/2001 12:23 PM

To: James.Dolan@pharma.com
cc: Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT, John M
Leonard/LAKE/PPRD/ABBOTT@ABBOTT, Larry L Lin/LAKE/PPD/ABBOTT@ABBOTT, Christopher J
Silber/LAKE/PPRD/ABBOTT@ABBOTT, James L Tyree/LAKE/ABBOTT
Subject: Re: ABT-594 - Purdue Response

Jim:

Thanks for your voice message and your e-mail note back. Your prompt response is most appreciated.

Purdue's position on the opportunity is most clear and its elucidation is both appreciated and respected. We look forward to potentially resuming discussions with Purdue when results of the Phase II data become available.

To let you know Abbott's immediate plans regarding ABT-594, pending any change in direction from R&D management, Abbott will engage several other parties who, like Purdue, have expressed considerable and repeated interest in ABT-594 over the past few years. Their ultimate interest and the potential for reaching an agreement prior to the release of any phase II data is, of course, unknown.

Jim, thank you again for Purdue's ongoing interest in a potential collaboration. I look forward to potentially interacting further with you and your scientists in the months to come.

Best,

Bob

James.Dolan@pharma.com on 03/06/2001 10:17:16 AM



James.Dolan@pharma.com on 03/06/2001 10:17:16 AM

To: robert.weiland@abbott.com
cc: larry.lin@abbott.com
Subject: ABT-594 - Purdue Response

Bob

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Pl. Exhibit 107 3/16/07 RM

Re our conversation last week, which was in reference to my letter of Feb8, 2001. Responding to our preferred commercial position in our letter to develop/market exclusively, you pointed out that Abbott is not proposing to either out license or sell ABT-594. We understand this position. Moving forward, a partnership with an equitable split of costs/revenues is a model we have done successfully before. In this case, Purdue would not be able to commit to any commercial terms now, before the M99-114 data were available. Based on the estimate of a May/June readout of this study, we would be prepared to reengage with you at that point

I'll call again to follow this up.

Regards,

Jim Dolan
Purdue Pharma
203 588 7297
james.j.dolan@pharma.com

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McCarthy Deposition Exhibit 113

P's Exhibit FT



James W
Thomas /LAKE/PPRD/ABBO
TT

05/10/2001 08:44 AM

To Yiming Zhang/LAKE/PPRD/ABBOTT@ABBOTT

cc

bcc

Subject 594

fyl.....David thinks this will be the basic design for the
phase 1 study.

----- Forwarded by Robert C Harris/LAKE/PPRD/ABBOTT on 05/08/01 08:20 AM -----

Marleen H Verlinden

05/08/01 05:30 AM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT, Richard G
Granneman/LAKE/PPRD/ABBOTT@ABBOTT, Walid
Awari/LAKE/PPRD/ABBOTT@ABBOTT, James P
Sullivan/BEDFORD/ADD/ABBOTT@ABBOTT, Michael K
Blarnesen/LAKE/PPRD/ABBOTT@ABBOTT
cc: Robert C Harris/LAKE/PPRD/ABBOTT@ABBOTT, Jacqueline V
Buentello/LAKE/PPRD/ABBOTT@ABBOTT

Subject: 594

Dear all,

John has asked me to take on a role that is a little more active and involved than I had intended with regard to designing the plans for ABT-594. I am at an off-site meeting with him in Milwaukee today. Given the very tight time frame (literally a few days), I am asking my assistant to set up a meeting involving the addressees of this e-mail only. I hope you'll see a chance to make time available for it tomorrow or Thursday, perhaps if needed, at the end of the day, from 5-7 pm if calendars do not allow otherwise. We need to be highly focused and strategic in what we try to achieve, that is why I am asking the most experienced people to partake in this meeting. As you can see, the compound has not been given up on, but on the other hand it does not seem like there is money available for it at this time.

We need to base our plan, in my view, on strong Pharmacokinetic and statistical input. Unfortunately the design of the Phase II proof of concept study was a bit deficient in that it did not allow for blood sampling at the time of dose-escalation. We must make sure we do this this time around. Rick, is there any trial simulation that can help us here? The issue we need to get to is: We want to obtain efficacy of 300 mcg bid or better, but need to get around the nausea and vomiting, and hence the horrendous dropout rates.

Here are some initial thoughts:

Study #1: study of nausea and vomiting (primary objective): 2 weeks treatment, 30 volunteers per group, target dose in all groups is 300 mcg bid, 14 days treatment

- group 1: use titration scheme used in diabetic neuropathy study (escalation every other day, starting with 75 mcg) = anchor group for comparison with diabetes study
- group 2: use titration scheme as in diabetic neuropathy study but let every dose be preceded within 15-30 mins by 10 mg metoclopramide p.o. (a combined DA antagonist/acetylcholine releasing anti-emetic and prokinetic)
- group 3: use titration every other day, but go in 50 % steps, e.g. 50-75-100-150-200-250-300
- group 4: use titration every day, with steps of 25 mcg:
25-50-75-100-125-150-175-200-225-250-275-300

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P1. Exhibit 113 3/16/07 RM

- group 5= placebo

Record: onset and disappearance of nausea and vomiting. Record daily: intensity nausea on 100 mm VAS, immediately before intake of drug, and 15,30,45,60,120,180,240 min later. Record number of vomits and time with regard to drug intake.

Plasma sampling: before and at anticipated T_{max} after each dose escalation

Any other study?

John's question with regard to partnership: any ideas?

Mike, please already have a look at the budget and personnel requirements, based on above study assumption

----- Forwarded by Marleen H Verlinden\LAKE\PPRD\ABBOTT on 05/08/01 05:05 AM -----

John M Leonard
05/05/01 05:58 PM

To: Marleen H Verlinden\LAKE\PPRD\ABBOTT@ABBOTT
cc:
Subject: 594

Marleen: Can you describe for me what your plans are for the analysis and follow up for 594? I briefly mentioned to the Ex Comm and showed to Jeff the results from the phase II study. Since we do not have formal budgeting for the program, we need to come forward with a plan and an analysis of the study as well. One aspect of the work should be to consider the partnering option to see what that will do for us. As it is, the project is risky but intriguing. Please give me a sense of where you want to go with this. The difficulty will be with coming up with some budget numbers to advance the program. I would like for you to assemble some rough cut numbers to continue for the year for people, PARD, etc. You should probably also consider reserving some number of patient slots for as yet undescribed studies. I will be asked by the Ex Comm later this week what it will take to continue the program, so I would appreciate having some sense of what the range of numbers might be.

Thanks,

J

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McCarthy Deposition Exhibit 118

P's Exhibit GO



Bruce McCarthy

06/27/2002 02:05 PM

To: Marleen H Verlinden/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: Questions re goals

Marleen-

some questions/comments regarding the update of goals..

Financial Goals

Existing goals (for remaining within budget and headcount) reflect responsibility for 963, dilaudid, 089 and the discontinued anti-psychotic program. I would propose changing to budget and headcount for 089, 239 and depakote (based upon 2002 Update final numbers), although this only represents responsibilities for the latter half of 2002 (and would result in removal of responsibilities to date). If we somehow capture management within budget and headcount for 1st half year responsibilities, I'm not entirely sure how one would calculate this (could provide an estimate of what was spent through June vs 2002 plan, but probably won't be able to get all of this information for 963, 089, and dilaudid by July 3).

New Goals

The goals you have assigned are appropriate and I agree to the timelines. Of my 8 existing goals, however, only one is 963-related and due in the latter half of the year and one goal is no longer applicable (outlicense 594...I'm in the process of verifying that Dan Norbeck blocked the outlicense of 594). I would, therefore, have only two openings for goals (out of the three below). Perhaps we could include goal #2 below into the people management goal (for the same 10% weight the people management goal already has)?

SIP

For the people new to SIP, goals will be updated (or created in the case of Tom Cummins, a new employee) and those for the latter half of the year will be applicable (first half will be CPS, so performance-independent for first half). Ken is part of APEX (have asked Silber for PE).

Bruce.

Marleen H Verlinden

Marleen H Verlinden

06/23/2002 10:59 PM

To: Bruce McCarthy/LAKE/PPRD/ABBOTT@ABBOTT

cc:

Subject: goals and firmly committed deadlines

Bruce,

I understood from Mike Spengler that the first pass of revised goals is going to be on July 3. I need your revised goals, to reflect deletion of abt-963 goals pertaining to second half of this year and the new responsibilities.

Please include as one of the goals:

- Work with Commercial Franchise to revise and revamp Depakote Phase IIb and PHase IV strategies, by 09/2002
- Build Neurosciences development teams according to new GPRD model, by 08/2002

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Pl. Exhibit 118 3/16/07 RM

- Finalize and issue to senior management comprehensive Phase III Development Plans for ABT-089 and ABT-239, by 09/01/2002

Remember that you are required to have 8 goals, none less than 10 % effort. Original Goals with a deadline prior to June 15, 2002 should not be altered.

You will also need to ensure that Ken has his Jan-June performance reviewed by Chris Silber before July 3, and that you receive this evaluation in writing. Intent is to do the evaluation now, rather than to have to go back at the end of the year. It is of particular importance to those who enter SIP program now. Please make this happen

Marleen Verlinden, PhD
Division Vice-President
Global Pharmaceutical Development
Abbott Laboratories
200 Abbott Park Road, R42U, AP-30-3SW
Abbott Park, IL 60064-6145
Tel: +1-847-935-4096
Fax: +1-847-938 1629

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McCarthy Deposition Exhibit 119

P's Exhibit GR

Probability Assessment Worksheet**Program: ABT-594****Project: Neuropathic Pain**

Phase	Project Probability of Success ^b	Industry Average Probability of Success ^c	Rationale/Assumptions
Pre-Clinical ^a	100 %	50%	<ul style="list-style-type: none"> Pre-clinical phase completed. Compound has entered human trials.
I	100%	75%	<ul style="list-style-type: none"> Completed
II	45%	51%	<ul style="list-style-type: none"> Chris; P = 0.4 Bruce; P = 0.5 (+) Phase-2 study fully powered for P-2 @ 80% (+) Reasonable signal seen already, with positive reports continuing. (-/+ SE's, while apparent, still don't stop trial, however significant drop-out still occurring. Might still be possible to optimize drug to minimize SE's/AE's. This takes Chris' Phase-2 prob. closer to 0.5.
III	%	70%	<ul style="list-style-type: none"> (-) Some general misgivings about unanticipated failure modes, eg. Serindole & QTc, or carc. studies not yet complete, etc. Given success in Phase-2, reasonably optimistic; Chris; P = 0.6 - 0.7 Bruce & Mike; P = 0.7 - 0.8, Use P = 0.70 for combined Phase 3/reg.
Registration	%	90%	<ul style="list-style-type: none"> .
Ph. III/Reg ^a	70% ^e	65%	No input needed. Joint Pr = 0.32

Footnotes^aCompound is approved as clinical candidate, but has not yet entered human trials.^bEnter 100% if project has completed a given phase, or if phase is not applicable^cSource: CMR International^eMultiply project probability of success for Ph. III times project probability of success for Registration and enter here.

Probability Assessment Worksheet**Program:** ABT-594**Project:** Chronic Persistent Pain, phase-2 publication study

Phase	Project Probability of Success ^b	Industry Average Probability of Success ^c	Rationale/Assumptions
Pre-Clinical ^a	100 %	50%	<ul style="list-style-type: none"> Pre-clinical phase completed. Compound has entered human trials.
I	%	75%	<ul style="list-style-type: none"> NA
II	16%	51%	<ul style="list-style-type: none"> P = 0.32, joint Pr of neuropathic pain indication being approved for ABT-594 (see ABT-594: Neuropathic Pain project data) For the Phase-2 study only, Set P = 0.5 because... <ul style="list-style-type: none"> (+) This is proof-of-concept for publication, yet powered almost the same as required for registration. Necessary to have convincing story for M.D.s (-) Tolerability must be comparable to COX-2's (-) This is a non-standard O.A. trial and there may not be any proof of efficacy at higher doses. (-/+) There is no certainty that the doses needed will correspond to the marketed 594 doses (this, however, has been factored into the forecast) Overall probability of success = $0.32 \times 0.5 = 0.16$
III	%	70%	<ul style="list-style-type: none"> NA
Registration	%	90%	<ul style="list-style-type: none"> NA
Ph. III/Reg ^e	% ^e	65%	No input needed. Joint Pr = 0.16

Footnotes^aCompound is approved as clinical candidate, but has not yet entered human trials.^bEnter 100% if project has completed a given phase, or if phase is not applicable^cSource: CMR International^eMultiply project probability of success for Ph. III times project probability of success for Registration and enter here.